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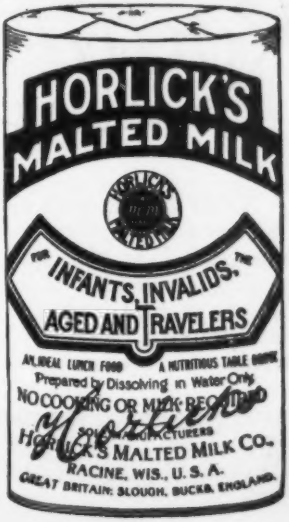
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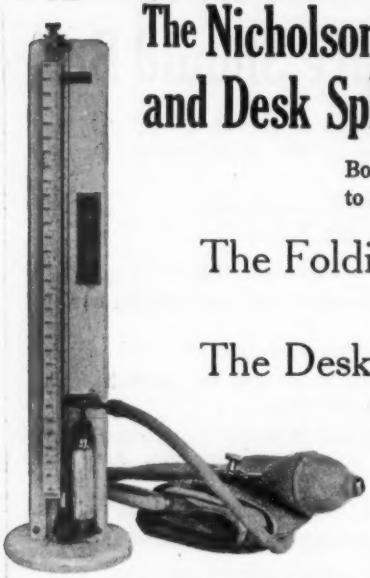

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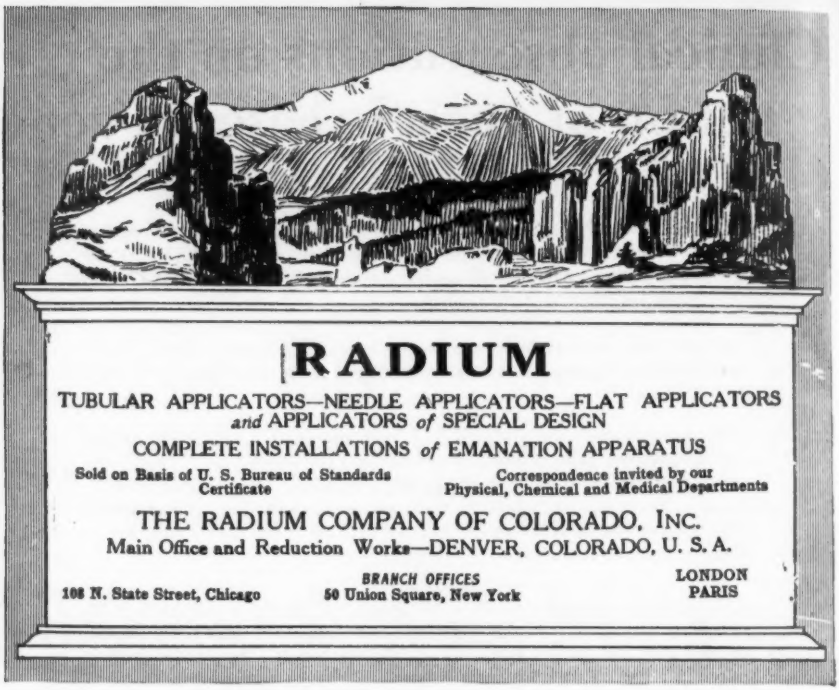

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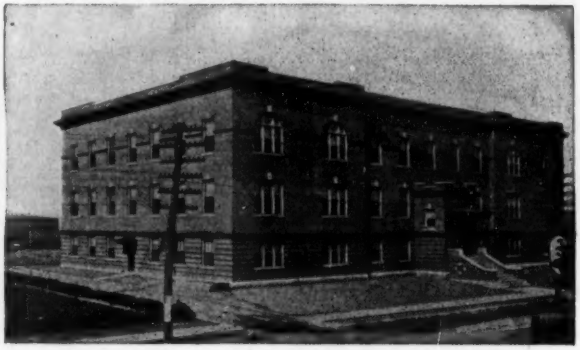

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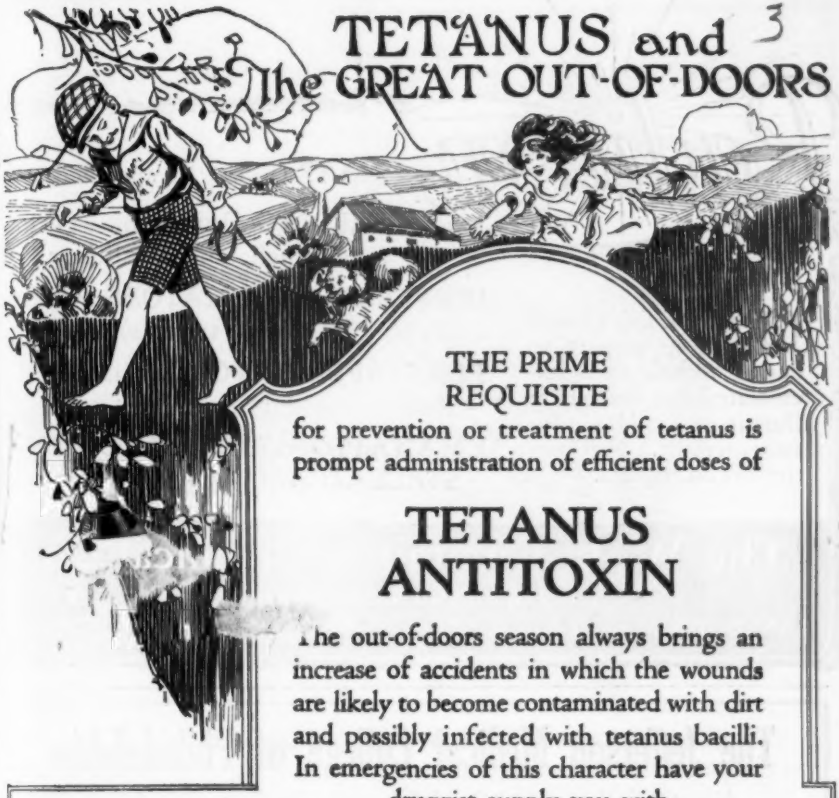

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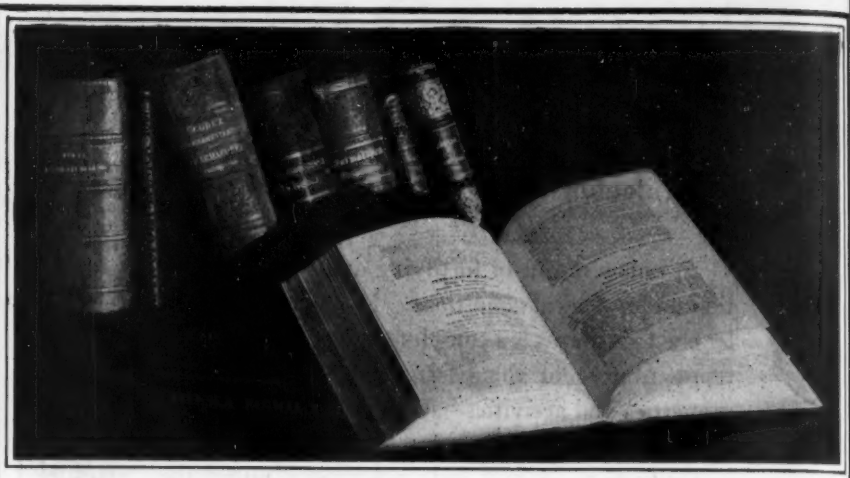

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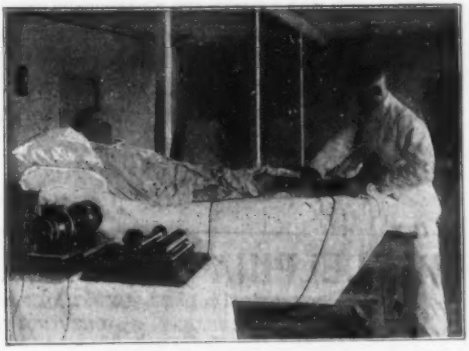

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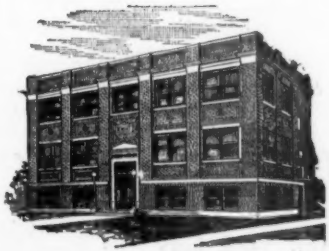

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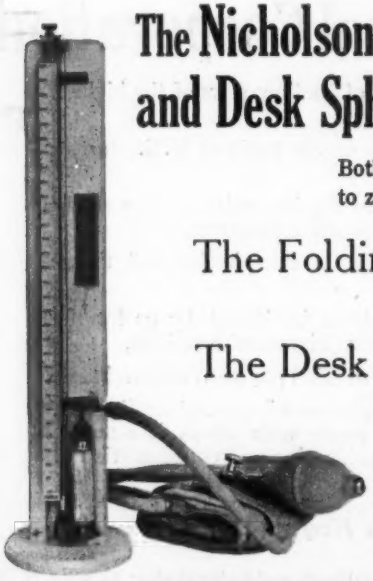

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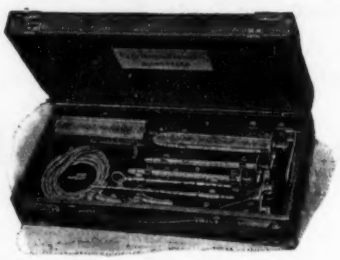

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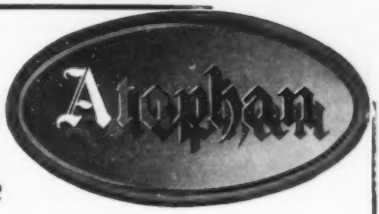

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JULY, 1920

ORIGINAL ARTICLES.

CARCINOMA OF THE PANCREAS.*

By Kellogg Speed, M.D.,
CHICAGO, ILLINOIS.

Along with our increase in knowledge of upper abdominal disease obtained from observation in the operating room and surgical research, we have made intense study of the gall-bladder and gall-ducts in the last few years. As more intimate knowledge of the anatomy and physiology became accepted, observers began to study the pancreas, especially in its inflammatory reactions and their relation to gall-tract disease. Very recently Deaver, Flexner, Opie and others have assumed that many of the pancreatic inflammations can be traced to lymphatic extension by continuity from the inflamed gall-tract glands or lymphatics. We have also learned by experiment and clinical observation that bile forced into the pancreas by way of its ducts may set up pancreatitis. When gall-stones or gall-bladder inflammation are present we can anticipate finding infections of varying virulence, and pancreatitis has become one of our every-day diagnoses in the upper abdomen. Formerly we thought little of this gland from a surgical diagnosis standpoint except in those rare instances of fulminating attacks of pancreatitis generally recognized when an acute abdomen was opened and the pathognomonic spots of fat necrosis were found on the omentum and peritoneal surface. We now know also that ligation of the pan-

* Read before the Chicago Surgical Society, February 6, 1920.

creatic ducts does not lead to fat necrosis of either the organ itself or the abdominal contents. Retention of the secretion which must follow is cared for by absorption into blood and lymph streams and the pancreatic ferments are rendered harmless.

Carcinoma of this organ has, of course, been studied and several series of cases been reported in the past. In the light of our progress in upper abdomen pathology and diagnosis it seemed that a study of pancreatic cancer might be of some value in furthering knowledge of this interesting gland. My interest has been sharpened by five patients of my own suffering from this disease and I have collected the statistics of the instances of cancer of the pancreas in the County Hospital, Chicago, occurring in the last six years. Altogether I have tabulated 52 cases of primary pancreatic cancer. Over half of these were clinical diagnoses made by the responsible attending staff of the hospital.

In the 52 cases at hand the average age at the time of diagnosis of primary cancer was 57 years, the youngest was 36 years, the oldest 76. Primary carcinoma of this organ has been found in an infant of 2 years by Herringham among the 17 cases occurring in St. Bartholomew's Hospital in 11 years. He found an average of five men afflicted to 1 woman; our series gives 36 males to 16 females.

In a series of cases collected by Herringham from the literature, the duration of the disease from the time of its recognition in 20 patients was not longer than 4 months; 33 of our patients died in the hospital, with an average stay of but 22 days. The average time of onset of symptoms before hospital admission was a few weeks, in some instances but a few days.

The most constant symptom found in our series is cachexia. This was present in 90 per cent. of the patents at time of admission and involved a weight loss of a few pounds to 80 pounds. This symptom appears to be very important; the loss is so rapid and unremitting that the disease should be suspected whenever rapid reduction in weight is mentioned by the patient. Its cause may be the loss of fats in the stools, a marked anorexia which most cases suffer, hemorrhages or a great distaste for fats commonly manifested. Because such a small percentage of these patients showed glycosuria, and as acetone and oxybutyric acid are so rarely found in the disease, the loss of weight cannot be attributed to excess oxidation in the tissues.

In order of frequency the next common symptom is jaundice, which occurs before the patient seeks medical advice, and is often the symptom which alarms him. Once inaugurated it is progressive and extreme, presenting all the symptoms of an intense cholemia. We found it in 80 per cent. of the cases on admission. Rarely an anomalous course of the common duct may account for absence of this finding.

Pain is the third prominent symptom, usually of cardialgic or gastralgic character, present in 61 per cent. of the admissions. The

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pain is frequently colicky at first and is often felt just preceding the onset of jaundice. We may imagine that the compression in the common duct by the cancer in the pancreatic head produces this obstructive jaundice and the backed-up bile distends gall-tracts and gall-bladder, with resulting colic. I recall one case of pancreatic cancer seen during my internship in the County Hospital in which the gall-bladder was extremely dilated and its peristaltic contractions could be seen through the emaciated abdominal wall. After a few weeks the pain becomes duller in character, may be gnawing, is quite constant and is frequently referred to the back. Those patients operated on for relief of the jaundice recovered from this pain in a large proportion.

Personal knowledge on the patient's part of an abdominal tumor mass or its discovery on examination was the next common finding in order; 55 per cent. of our patients had a mass either in the liver or some part of the midepigastric region. Most frequently this mass was liver enlarged by bile or metastases or the overdistended gall-bladder. In a small percentage of patients the tumor was felt in the pyloric region and was the pancreas itself or an extension of its cancer into the stomach or the neighboring organs. The pancreatic mass is not moved by respiration; it lies behind the inflated stomach or colon and was felt best after abdominal tapping in those patients who presented ascites.

Ascites was present in approximately 20 per cent. of the patients, as was also hemorrhage, which occurred in 11 patients, 2 of the mouth, 4 of the nose, 1 of the bowel, 2 in the buttocks and skin and 2 of the stomach. Hemorrhages within the alimentary tract or abdomen are most often caused by pressure of glands or carcinoma, varices resulting which burst. Malignant ulceration is also found as a cause. Skin hemorrhages are found most often in those patients with fat necrosis; the removal of calcium which combines with the fatty acids acting with jaundice causes blood changes which result in hemorrhage. Our patients did not show petechiæ, which are mentioned as a prominent finding in the disease. One instance of ascites was a pure chylous ascites caused by pressure stenosis of the receptaculum chyli from enlarged glands.

Constipation was mentioned in 19 of the 52 patients; diarrhea occurred in but 3.

Edema of the lower extremities occurred in 6 per cent. of the patients. Both ascites and extreme edema are caused by pressure, except a few instances of carcinomatosis of the peritoneum.

Gastro-intestinal roentgen-ray examination was made of 23 patients and a correct diagnosis was arrived at in but 2, the fluoroscopic and plate examination showing little positive findings except displaced stomach or intestine with no obstructions or filling defects.

The urine of 3 of these patients showed sugar and one showed acetone. Bile, of course, was found in all the jaundiced patients.

The feces were not always examined. They showed blood in 30 per cent. of the total number of cases and excess free fat in 15 per cent. The stools were frequently bulky from fat and undigested material.

Stomach analyses were also not always possible, but in the 26 patients examined, 21 showed a normal or slightly increased acidity while 5 had a reduced amount of acid. The motor power and digestion of the stomach were usually good.

Steatorrhea, or the finding of excess fat in the stools, was not a constant nor reliable symptom. I refer to it only to mention that physiologically an individual may excrete up to 20 per cent. of all ingested fat and still be within normal limits. Likewise azotorrhea, or the finding of undigested proteid material, usually meat fibers, is inconstant and unreliable. We know that whenever the bile is taken away from the intestinal contents at the ampulla of Vater or in acute diarrheas there follows disturbance of fat digestion and absorption. If, however, a patient with or without jaundice shows both steatorrhea and azotorrhea it is highly presumptive that the external secretion of the pancreas is failing. These symptoms are also late in the course of the disease.

Various laboratory tests have been announced which have been claimed as pathognomonic for primary pancreatic cancer. The elaborate Cammidge test and the Loewi test of adrenalin in the conjunctival sac have both been proved erroneous. No pathognomonic pancreatic symptomatology can be expressed because the disease of this organ is too often overshadowed by symptoms of involvement of the neighboring structures, stomach, duodenum, gall-tracts and colon.

Of our cases 11 went to autopsy. The head of the pancreas is most often involved in cancer, the body next and the tail least often. Not one showed pancreatic calculus. Stone has been considered an exciting cause of gall-tract carcinoma. There are a few cases in the literature of pancreatic stone associated with primary cancer of the pancreas. If carcinoma is confined entirely to the tail and left side of the body and does not involve the common bile duct by pressure, we may find no symptoms at all until the patient is near the end and emaciation and extensive metastases are in evidence.

Our autopsy records show that metastases are usually first in the lymphatic glands around the pancreas and gall-tract areas. The liver, of all neighboring organs, is most often invaded. The stomach, colon, spleen, kidneys, and thoracic organs may be involved. One of our cases showed carcinomatous involvement of the eighth dorsal vertebra, one a chylous ascites, and several a general carcinomatosis of the peritoneum, abdominal and thoracic organs.

The common gall-duct is embraced completely in the head of the pancreas in 62 per cent. of human cadavers; in the remainder it lies in a deep groove in the head of the gland. Consequently cancer of

the pancreatic head involves the common duct by pressure, with resulting jaundice and gall-bladder dilatation. High intestinal obstruction, pyloric obstruction, large bowel obstruction, thrombosis of the mesenteric vessels and resulting bowel gangrene, aneurysm of the aorta or external pancreatic fistula may be found. We can understand that when the two ducts of the pancreas are occluded the disturbance of digestion from lack of the three ferments secreted by the pancreas will follow, but every cancer will not involve the head and the two ducts, hence the symptoms are variable. Likewise it has been found, on microscopic examination, that there is great and true hypertrophy of the cells of the islands of Langerhans, which may explain the infrequency of glycosuria as found in this series. Those islands remaining uninfluenced by the carcinomatous process take on extra duty and maintain a carbohydrate equilibrium by their increased internal secretion. Functional disturbance of the pancreas is not evidenced until the greater portion of the gland is affected. Usually if diabetes has developed the surgeon is too late to offer assistance.

Wright found accessory pancreas near the umbilicus in connection with the persisting remains of the vitelline duct. An accessory pancreas may account for lack of glycosuria and also for the development of primary cancer. These accessory glands have been found by or inside of the duct of Santorini, in the walls of the stomach, duodenum, jejunum or ileum, with small independent ducts opening into the contiguous bowel.

Pathologists have had some discussion over the cell origin of pancreatic cancer. Finding the greatly enlarged and heavily staining cells of the island of Langerhans misled them into believing that these cells may be those forming the cancer (Fabozzi). It was supposed that glycosuria was so seldom present because the cancer cells, taking their origin from the island of Langerhans, retained their power of forming an internal secretion which controlled carbohydrate metabolism. To distinguish between primary carcinoma of the duodenum and bile ducts histological study is necessary. Ewing says that carcinoma of the pancreatic ducts follows periductal fibrosis and carcinoma of the parenchyma appears after interstitial fibrosis. Two types of cells are found: one cylinder-celled adenocarcinoma arising from the ducts as papillary outgrowths and second, carcinoma simplex, arising from the parenchyma, usually scirrhous in type.

Surgical treatment is difficult to apply to patients suffering with carcinoma of the pancreas. The anatomical position of the gland, while quite accessible, is one which invites disaster to proximal organs and structure if pancreatectomy is performed. Cysts and encapsulated tumors of the pancreas have been successfully removed by either the abdominal or lumbar route, but I have not found in the literature successful complete pancreatectomy in cancer of the

pancreas. Some operators have considered that they have performed complete pancreatectomy, but autopsy has disproved their belief. Partial pancreatectomy can be successfully done. We must recall that a large percentage of these patients are deeply jaundiced. Blood coagulation time is greatly increased, up to eight or even ten minutes, so that operative procedures are hazardous. The leaking of pancreatic secretion after operation into the abdominal cavity always results in death. Exudate from the injured pancreas, which is not the normal secretion, prevents the formation of salutory peritoneal adhesions, and catgut stitches are rapidly digested. Pancreatic juice mixed with blood is very toxic, and when introduced into the peritoneal cavity will cause death without the aid of bacterial infection. We must also remember the anatomical relation of the common duct, stomach, aorta, colic arteries, duodenum, large bowel, kidneys and spleen.

Palliative treatment is possible. To relieve the backing up of gall we can drain the gall-bladder. Patients do poorly after this operation and usually die within a few weeks. Cholecystgastrostomy returns the bile to the intestinal tract, as also does cholecystenterostomy. I prefer the latter, because if the gall-bladder is connected to the stomach, pyloric or duodenal obstruction may arise from pressure or extension of the cancer, and then a gastroenterostomy would be needed in addition. All these operations are represented within this series. Thirteen of our patients were operated on, mostly for gall-bladder drainage or removal; 4 of these were later examined at autopsy. At this time I have one patient with primary carcinoma of the pancreas alive four months after a cholecystenterostomy. The gall-bladder is usually so large, grape fruit size or larger, that it is not difficult to anastomose it to the stomach or intestine.

The matter of diagnosis is most interesting. Of these 52 patients a correct diagnosis was made in only 3 instances when the patient was first examined. Among admission diagnoses were the following: cholelithiasis, cholecystitis, carcinoma of the stomach, cirrhosis of the liver, organic heart disease and pulmonary tuberculosis.

In all patients with a deep jaundice, with cachexia or obscure upper abdominal symptoms, when a positive diagnosis cannot be made, we should consider the pancreas, and especially carcinoma, in those of mature age when there is no history of gall-stones or previous febrile attacks. If the gall-bladder is enlarged, with or without changes in the liver size, if there are tumor masses, or any of the other symptoms enumerated, we are probably dealing with the pancreas.

Also, I believe when we are performing operations in the gall-tracts or pyloric region we should always palpate this deeper lying organ. Several of the patients in this series were operated on for removal of the gall-bladder without investigation of the pancreas. The true

condition was revealed at autopsy. The gall-bladder removal takes away our best means of offering palliative treatment, because there then cannot be performed any circuiting operation to keep the bile within the individual's alimentary tract, and failure from continuous bile drainage is rapid. When the bile is returned to the intestines we may see a temporary gain of weight and strength and some prolongation of life, an extension of a few months or a year. There is, moreover, no mussy bilious fistula which requires constant attention; the patient can be up and about with a closed abdomen.

ANATOMIC DIAGNOSES IN ELEVEN POSTMORTEMS.

1. Hammond. Date of autopsy, March 30, 1915. Examiner, Bissell. Carcinoma of the pancreas and stomach; generalized metastatic carcinomatosis of the peritoneum; marked emaciation; ascites; therapeutic paracentesis middle puncture wound of the abdominal wall; moderate edema and passive hyperemia of the lower lobe of the right lung; compensatory marginal emphysema of the left lung; moderate fatty changes in the myocardium, liver and kidneys; cloudy swelling of the liver and kidneys; multiple retention cysts of both kidneys; right-sided obliterative fibrous pleuritis; moderate edema of the cerebral cortex; hyperplasia and anthracosis of the tracheobronchial lymph glands; missing teeth.

2. David Rhodes. Date of autopsy, June 2, 1915. Examiner, Wells. Primary carcinoma of the pancreas, with extensive secondary involvement of the retroperitoneal thoracic lymph glands, with extension into the stomach, ileum and cecum, with secondary ulceration; massive secondary in omentum, metastases in liver and lungs, parietal and visceral pleura, diaphragm, adrenals, perirenal tissues and subcutaneous tissue and spleen and myocardium; senile arteriosclerosis; parenchymatous nephritis; ascites; edema of lower extremities; pseudomelanosis of the intestines; edema of the lungs; calcification of the trachea and bronchi.

3. Herman Strehlow. Date of autopsy, August 3, 1916. Examiner, Nuzum. Primary carcinoma of the pancreas; metastatic carcinoma of the retro-aortic, iliac, lumbar and mesenteric lymph glands; carcinomatosis of the peritoneum; pressure stenosis of the receptaculum chyli at the level of the second and third lumbar vertebræ by hyperplastic cancerous lumbar lymph glands; true chylous ascites; marked pressure stenosis of the pyloric sphincter of the stomach by the carcinomatous pancreas; chronic dilatation of the stomach; varicosity of the veins of the cardiac orifice of the esophagus; free tarry black blood in the stomach and bowel; emaciation; compensatory varicosity of the superficial veins of the chest, abdomen and the right thigh; bilateral hydrohemothorax; marked edema and passive hyperemia of the lungs; latent healed and encapsulated fibrous apical tuberculosis; right-side focal adhesive pleuritis;

tuberculous cervical adenitis; ancient healed surgical incisions of both sides of the neck; fatty changes in the myocardium and liver; terminal edema of the scrotum and lower extremities; gold capped tooth; work-worn hands.

4. Andrew Nikolick. Date of autopsy, November 9, 1916. Examiner, Nuzum. Primary carcinoma of the head of the pancreas; metastatic carcinomatosis of the liver, left lung, pericardial sac, ribs and lymph glands generally; icterus; clay-colored stools; frank lobar pneumonia of the right upper lobe (gray hepatization); section wound in hollow of right arm; work-worn hands.

5. Susie Magree. Date of autopsy, June 13, 1913. Examiner, Harms. Carcinoma of the pancreas, with metastases in the liver; mitral insufficiency; hypostasis of the lungs.

6. Luke Moore. Date of autopsy, April 6, 1917. Examiner, Nuzum. Primary carcinoma of the pancreas; metastatic carcinomatosis of the perigastric, biliary and peribronchial lymph glands; secondary carcinoma of the liver, lungs and adrenals; marked varicosity of the esophageal veins at the cardiac orifice of the stomach; ruptured esophageal vein; free and clotted blood in the stomach and small bowel; marked anemia; icterus; ascites; marked passive hyperemia and edema of the lungs; missing teeth.

7. Murray Catlin. Date of autopsy, August 28, 1917. Examiner, Le Count. Primary carcinoma of the body of the pancreas; secondary metastatic carcinoma of the liver, peritoneum and bowel; ulcerative carcinoma of the liver, peritoneum and bowel; ulcerative carcinomatous enteritis; edema evacuo (carcinomatous cachexia) of the subpericardial adiposæ tissue; pressure kinking of the splenic artery (carcinoma); mural thrombosis of the splenic vein; infarction of the spleen; marked anemia; moderate emaciation; sordes of the lips; chronic diffuse nephritis; secondarily contracted kidneys; submucous fat infiltration of the renal pelves; arteriosclerosis of the aorta and front mitral leaflet; fibrous myocarditis; brown atrophy of the myocardium; senile emphysema of the lungs; barrel-shaped chest; patent foramen ovale; hypertrophy of the left heart; huge edema of the leptomeninges; disseminated atrophy of the cerebral cortex; foramen magnum pressure furrow of the brain stem; marked hypostatic hyperemia and edema of the lungs; lessened yellow material of the adrenal glands; slightly fatty liver; fatty changes of the lining of the aorta and carotid arteries; epicardial fat infiltration of the heart; fibrous pleuritis; calcification of the tracheobronchial lymph glands; small traction diverticulum of the esophagus; external fibrous epicardial patch; fibrous adhesions between the right lobe of the liver and the fatty capsule of the right kidney; ossified costal and thyroid cartilages and falx cerebri; arcus senilis; marked coal-dust pigmentation of the lungs and tracheobronchial lymph glands; nodular glandular hyperplasia of the prostate gland; plaques jaunes of the left frontal lobe of the cerebrum; cavities;

absence of some teeth (caries); circumcised penis; hairy body; pigmented mole of the trunk; scar of the skin of the left knee; post-mortem digestion of the lining of the esophagus.

9. John Hermanson. Date of autopsy, May 10, 1918. Examiner, Davis. Primary carcinoma of the head of the pancreas; generalized icterus; biliary cirrhosis of the liver; clotted blood in the large and small bowel; marked anemia; bile staining of the kidneys; right-sided obliterative fibrous pleuritis; hypertrophy of the heart; slight senile arteriosclerosis; fibrous adhesions between the gall-bladder and the liver; left-sided inguinal hernia; calcification of the thyroid cartilage; superficial healing abrasion of the right elbow; fibrous adhesions between the greater omentum and the parietal peritoneum anteriorly; carious teeth.

10. Sam Rhys. Date of autopsy, June 25, 1918. Examiner, Nuzum. Primary carcinoma of the head of the pancreas; dilatation of the common, cystic and hepatic ducts; cholelithiasis; moderate icterus; moderate tawny yellow atrophic cirrhosis of the liver; slight diffuse nephritis; acute vegetative endocarditis of the aortic valve; marked senile disseminated arteriosclerosis; sclerosis of the aortic and mitral valves; sclerosis of the coronary arteries; caseous tuberculosis of the upper lobe of the right lung; healed bilateral apical tuberculosis; bilateral apical fibrous pleuritis; fibrosis and hyperplasia of the peribronchial lymph glands; right inguinal hernia; carious and missing teeth.

11. Frank Turanek. Date of autopsy, September 14, 1918. Examiner, Nuzum. Primary medullary carcinoma of the head of the pancreas; secondary carcinomatosis of the peripancreatic, perigastric and retroperitoneal lymph glands; secondary carcinoma of the bile ducts, gall-bladder and liver; free and clotted blood in the small bowel; hemorrhagic ascites; slight icterus; bile staining of all the viscera of the body; moderate hyperplasia of the spleen; multiple petechial hemorrhages in the renal pelves; old healed fibrous tuberculosis of the apex of the right lung; latent caseous and calcified tuberculosis of the peribronchial lymph glands; right-sided obliterative fibrous pleuritis; disseminated scratch marks of the skin of the body.

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THE THERAPEUTIC USE OF OXYGEN.[1]

By R. D. Rudolf, M.D.,
TORONTO, CANADA.

Oxygen has been used as an inhalant occasionally for many years, but its efficacy has always been doubted by many, chiefly on the theoretical grounds that as the oxyhemoglobin of the blood is already nearly saturated, no increase in this can be obtained by the mere raising of the percentage of oxygen in the inhaled air. A further objection has been urged that the oxygen may act as an irritant to the respiratory passages. It may be as well to dispose of this objection at once. It is quite true that if animals be placed for a short time in an atmosphere which contains three atmosphere pressures of oxygen they soon contract pneumonia, and, further, Lorrain Smith has shown that this also occurs if animals are kept for several days in an atmosphere of pure oxygen; but it has also been shown that an atmosphere of pure oxygen can be breathed for

[1] Read before the Academy of Medicine, Toronto, February, 1920.

many hours without any evil effects, and also that, an atmosphere containing under 70 per cent. of oxygen can be breathed with impunity for any length of time.[2] Thus we need have no fear that in giving inhalations of oxygen for ten to fifteen minutes at a time we are running any danger of causing irritation of the air passages.

In recent years much work has been done on oxygen by such men as Haldane and Leonard Hill on the physiological side, and clinically its value has been greatly enhanced by the experience of the War. In the acute respiratory inflammations produced by enemy gas, nothing proved so useful in giving relief as did oxygen. Lately, Dr. Meltzer, of the Rockefeller Institute, has written strongly urging its value in pneumonia. Using a special apparatus, which I will presently demonstrate, he has shown that such cases may not only be symptomatically relieved, but that life may be saved in some apparently hopeless instances.

Looking first of all at the physiological side of the question, it is undoubtedly true that when a healthy individual is breathing quietly the percentage of oxygen in ordinary air (about 20 per cent.) is not only enough to sufficiently saturate his hemoglobin and to supply the needed partial oxygen pressure in his blood plasma (which is about one-fortieth of that of the hemoglobin), but the percentage of oxygen in the inhaled air may be reduced to perhaps 14 per cent. without causing any distress to the patient. In other words, the atmosphere contains a higher percentage of oxygen than is required for the needs of the healthy resting individual. But let that individual exert himself, and soon he will become breathless, and then it is found that an increasing of the oxygen content of the air will help him. This has been abundantly proved by Leonard Hill and others, who have shown that a man can do more physical work without distress if he is breathing an atmosphere artificially enriched with oxygen than if he is depending upon the ordinary air. Evidently the difference between the 14 per cent., which is all the oxygen that a man at rest requires, and the 20 per cent. of the ordinary air is, as Meltzer puts it, a "factor of safety," and while this factor of safety is sufficient for meeting the increased demands of ordinary exertion, it is not enough for emergencies. A man suffering from some interference with his respiration may be likened to the healthy one undergoing extra exertion.

Further, at high altitudes the partial pressure of oxygen may be less than that of an atmosphere containing only perhaps 14 per cent. of oxygen, and here there is no margin of safety, and the least exertion may bring on symptoms of want of oxygen (often very suddenly), and, of course, if a still higher altitude is attained, as is often done by airmen, then these symptoms will come on without any exertion.

[2] Flack and Hill: Text-book of Physiology, p. 304.

Again, it has been found that at altitudes of 6000 feet and over cases of pneumonia do very badly,[3] this factor of safety being now missing. Haldane says here: "Even in ordinary cases of croupous pneumonia the alveolar oxygen pressure may be a matter of decisive importance. This is clearly shown by the fact that these pneumonias do very badly at high altitudes. At Cripple Creek (altitude, 10,000 feet), in the Rocky Mountains I found that this was so well recognized that all cases of pneumonia were put on the train and sent down to the prairie level."[4]

Oxygen is very essential to the living tissues. As a leading writer in the *British Medical Journal* says, "A man may go for weeks without food, for days without water, but for seconds without oxygen.[5]

Anoxemia is the term applied by Haldane to "the condition when the rate of supply of oxygen is insufficient for the normal carrying on of life."[6] The causes of it are four: (1) Defective saturation of the arterial blood with oxygen; (2) slowing of the circulation; (3) defective proportion of available hemoglobin in the blood; (4) an alteration of the dissociation curve of the oxyhemoglobin, so that this gives off its oxygen less easily than usual.

Most of these causes are evident. For example, any decrease in the oxygen pressure in the inspired air, or any interference with the passage of air to the blood from outside, will produce a defective saturation of the arterial blood with oxygen, as will also any increased using up of the arterial oxygen if a new supply be not immediately available.

Slowing of the circulation will tend to anoxemia both by allowing the blood to dwell too long in contact with the tissues and also by delaying its return to the lungs for recharging.

Anemia means a want of hemoglobin in the blood, and poisoning with carbonic oxide gas with nitrites and with arseniuretted hydrogen will prevent the carrying of oxygen by the hemoglobin.

The alteration of the dissociation curve of the oxyhemoglobin is a less evident cause of anoxemia. Bohr, of Copenhagen, showed that if the carbonic acid in the blood be lowered the hemoglobin tends to cling to its contained oxygen, and thus the peculiar condition may exist of an anoxemia with the hemoglobin laden with oxygen which it will not part with.

As regards the relation of anoxemia to cyanosis it may be said that cyanosis always means anoxemia (the hemoglobin being more or less in the form of reduced rather than oxyhemoglobin); but while anoxemia is generally accompanied by cyanosis, this is not necessarily the case: for example, in carbonic-oxide poisoning the blood is cherry red, and yet the patient may die of want of oxygen. Again, when the carbonic acid is deficient, the tissues may be suffering from

[3] Sewall, Henry: Forchheimer's Therapeutics, vol. i, p. 281.
[4] British Med. Jour., February 10, 1917, p. 182.
[5] Ibid., July 19, 1919, p. 81. [6] Ibid., p. 65.

anoxemia, and yet the blood may be red with hemoglobin, which will not part with its oxygen (according to Bohr's law) because of the lowness of the CO_2.

Respiration depends upon two main factors: (1) the presence of sufficient CO_2 in the blood and (2) a want of oxygen. Normally the CO_2 in the alveolar air of the lungs is about 5.6 per cent. of this air, and the least rise in this percentage causes such a stimulation of respiration that the percentage is quickly reduced. On the other hand a slight fall causes the condition of apnea, and then in consequence the percentage quickly rises again. The CO_2 acts through the blood by stimulating the respiratory center.

The effects of fluctuations in the percentage of oxygen in the alveolar air are not nearly so great. Want of oxygen does cause increased breathing, but only to a slight extent. It is possible for a person to be blue from want of oxygen and yet have no increase in respiration if the CO_2 be lower than it should be. But the respiratory center consists of cells which require oxygen for their proper function, just as do all the cells of the body, and when the oxygen in the inspired air is sufficiently reduced the respiration becomes weak and then fails. As Haldane says, "One of the most important effects of prolonged or extreme anoxemia is a temporary partial failure of the respiratory center, so that oxygen or even artificial respiration may be required for many hours."[7]

I have seen this fact beautifully demonstrated by Professor Macleod in the physiological department of our University, where the tracing of the respiratory movements of an animal deprived of oxygen shows gradual failure which quickly disappears when oxygen is again administered.

It is well to remember that after all it is the amount of oxygen in the blood plasma that really counts. Usually this is only about one-fortieth as much as is contained in the hemoglobin, but as it is used up in the tissues it is constantly replaced from the red cells. Normally, 100 c.c. of plasma contains only about 0.35 c.c. of oxygen in solution, the balance of the oxygen in the blood being combined with the hemoglobin; but it is possible by increasing the oxygen in the inspired air sufficiently to raise the oxygen in solution in the plasma to nearly 3 c.c. per 100 c.c. For example, if the oxygen in the alveolar air be raised to 36.4 per cent., that in the plasma will stand at 0.945 per cent., and if the alveolar oxygen be 86.7 per cent. that in the plasma will be 2.26 per cent. This is always assuming that the pulmonary epithelium is passive. Thus it is possible to increase the partial oxygen pressure in the plasma some seven times by merely raising the percentage of oxygen in the inspired air. After all, the red cells are merely carriers, and it is the oxygen in the plasma that directly feeds the tissues. "One well-known proof

[7] British Med. Jour., July 19, 1919, p. 69.

of this consists in replacing the blood in a frog with physiological saline solution and then subjecting the frog with the saline in its bloodvessels to an atmosphere of pure oxygen, when it will be found that the animal continues to absorb the normal amount of oxygen and exhale the normal amount of CO_2. It respires normally without any blood in the bloodvessels."[8] The plasma, like travellers during a strike of railway porters, may to a certain extent do its own carrying.

The effect of anoxemia on the vital tissues is drastic. If the oxygen pressure be low enough then these tissues quickly die; but short of this they may be fatally damaged, as is seen when after CO poisoning an individual may die, although all the CO has again been replaced with oxygen. It is thus important to remember that anoxemia, which clinically is usually shown by cyanosis, is a damaging condition, especially to the nervous and circulatory tissues, and hence should be relieved as quickly as possible, not only for the immediate relief given but also for the sake of the future life and health of these tissues. It has been recently pointed out by Meakins, Priestly and Haldane[9] that in many cases in which the respiration is shallow but rapid the patient is insufficiently ventilating his lungs, although breathing a great deal. Here a vicious circle is liable to be established, the anoxemia making the breathing shallow though rapid and the shallow breathing increasing the anoxemia. Rapid breathing often denotes an insufficient breathing just as a rapid heart may mean a weak heart. Cheyne-Stokes' breathing is a sign of a failing respiratory center and may usually be at least temporarily removed by inhalations of oxygen.

Thus from a clinical point of view, whenever a patient is cyanosed and usually whenever he is breathing very rapidly he is more or less in a state of anoxemia, and we should try to relieve this by increasing the percentage of oxygen in the air that he breathes. Haldane says, "Cyanosis may always be taken as an indication that oxygen inhalation should be considered." There are, of course, two kinds of cyanosis: (1) The leaden color of the skin often seen in acute respiratory conditions, when the oxyhemoglobin is reduced, and yet the veins are not overfull, and (2) the blue color of the mucous membranes, in which the veins are distended with this reduced blood. In this latter type venesection is often called for, followed, if necessary, by oxygen.

Methods of Giving Oxygen by Inhalation. I may say here in parenthesis that oxygen has been administered subcutaneously, intravenously and into the cavities of the body, but we are only now dealing with its use as an inhalant. Perhaps the commonest way of giving oxygen is to hold a funnel connected with the oxygen cylinder near to the face of the patient. This is a most unsatisfactory

[8] Macleod's Physiology, p. 378.

[9] Jour. Physiol., 1919, lii, 433.

way and scarcely deserves to be considered as oxygen administration at all. Meltzer has shown that it is not thus possible to raise the percentage of oxygen in the inhaled air by more than 2 per cent. Further, in a patient already short of breath the mere holding of a funnel close to his mouth and nose gives him a sensation of smothering, and he will often try in his agony to remove the apparatus. I have not used the Haldane apparatus, but it involves the placing of a mask over the patient's face, and hence has this objection, and Haldane himself says that the patient may try to remove it. The same objection applies to the apparatus of Leonard Hill. A much better method than this, and the one that we used most extensively overseas, was the giving of the oxygen through a soft rubber tube inserted into one nostril and held in position by a strip of strapping. This is a wasteful way of giving the gas, but very efficient, and the patient does not object. Its efficacy can be greatly increased if an attendant rhythmically closes the opposite nostril during each inspiration.[10]

A third way of giving oxygen is by the use of the oxygen chamber. I saw this method last year at Cambridge, where Dr. Barcroft and his assistants were experimenting with it. They had three chambers in use. These were made specially for the treatment of late gassed cases, but as the Armistice had come before many soldier patients had been treated they were continuing the work on other conditions. The oxygen content of the atmosphere in the chambers was maintained at 40 to 50 per cent., any excess of CO_2 and moisture being removed by suitable agents. The patients were kept in the chambers from 5 P.M. until 10 A.M. next day for five consecutive days. Great improvement in their condition was evidenced by the removal of the nocturnal dyspnea, from which they nearly all suffered, by a greater capacity for physical work during the day and by the removal of the polycythemia, which was usually present. Several British hospitals have had such oxygen chambers erected as part of their equipment, notably at Guy's and at Stoke-on-Trent, and hope is held that many patients will be much benefited by their use. I would like to see one in Toronto.

The last method that I will describe is that of Dr. Meltzer, of the Rockefeller Institute. The apparatus consists of a hollow tongue depressor which is placed in the patient's mouth and is connected with a gas bag filled from an oxygen cylinder. A valve is so placed that during inspiration the oxygen under pressure from the elastic walls of the bag enters the patient's mouth, while during expiration the oxygen flow is checked and a large opening appears near the valve through which the patient exhales. This valve is worked rhythmi-

[10] Using this method with Professor Macleod, we found that his alveolar oxygen was raised to over 20 per cent. when the tube was in one nostril and the other nostril left open, while when the other nostril was rhythmically closed during each inspiration the oxygen in the expired air rose to 59.9 per cent.

cally by the thumb of the operator. By this arrangement the oxygen enters the air-passages under pressure during inspiration, while during expiration no resistance to the outflow of air occurs. Meltzer says[11] that Dr. A. L. Meyer, of the Rockefeller Institute, found that after he had been thus insufflated for eight minutes his expired air consisted of nearly pure oxygen, the nitrogen of the atmosphere being displaced by this gas. Professor Macleod and I tried this on him, and the analysis of his alveolar air after nine minutes' insufflation showed a percentage of oxygen of 34.6 instead of the normal of 16.5, and when we repeated the experiment, with the nose clamped so that he breathed entirely through the apparatus, the percentage of oxygen in the expired air rose to 86.7 per cent., which practically confirms Dr. Meyer's findings. Now, as before stated, a rise of the oxygen pressure in the alveolar air to 36.4 per cent. means a corresponding rise in the oxygen in the plasma to 0.945 per cent., and if the oxygen in the alveolar air stands at 86.7 then that in the plasma will be 2–26, or seven times the normal. The hemoglobin in a healthy man is already nearly saturated with oxygen and will, hence, not take up little more when it is offered to it through the raising of the percentage in the alveolar air. In fact, as already said, the inhalation of oxygen by the resting normal individual produces no results. The pulse-rate, respiration and blood-pressure remain unaltered and the individual has no subjective sensations. But in anoxemia the hemoglobin is not saturated, and in such cases we cannot only raise the oxygen percentage in the blood plasma, but also in the red blood cells, and hence the cyanosis tends to disappear.

Coming now to actual experience in the therapeutic use of oxygen I think that if it be properly given there is no doubt of its value in suitable cases. I say properly given, for if the administration consists in merely holding a funnel connected with the oxygen tank in front of the patient's face then the results will naturally be *nil*. As already said, in this way one cannot raise the oxygen in the alveolar air by more than 2 per cent., and, further, the patient probably objects to the apparatus, which interferes with his normal breathing. When the oxygen is given by the tube in a nostril great relief can usually be given. During the epidemic of influenza and pneumonia in England last year I frequently saw military patients who were breathing badly and cyanosed (even although being treated in the open air) improve visibly in a few minutes under this form of administration. Not only does the cyanosis lessen or disappear and the breathing tend to become slower and deeper, but again and again have I heard the patients express their great satisfaction at the relief given, and in such a definite disease as pneumonia the subjective improvement is of much significance and value. In some cases the cyanosis

[11] The Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, Jour. Am. Med. Assn., October 6, 1917.

is relieved and yet the breathing remains rapid, while in others the opposite is the case; but in most instances the cyanosis is lessened and the respiration slows. Thus in a patient insufflated recently by the Meltzer method the respiration fell from 32 to 18 and the slight cyanosis from which he suffered remained practically unaltered. Professor Hoover has called attention to the frequent dissociation of the anoxemia and cyanosis,[12] but it would serve no useful purpose here to go into details in regard to it. If the pneumonic patient is having much pleuritic pain he will often say that the oxygen has relieved it. I presume that the slowing of the breathing accounts for this.

It may be objected that oxygen insufflation is only symptomatic treatment and that the patient will soon relapse, but very often he may not do so for hours or not at all, and the treatment can always be repeated as required. As Haldane says: "It may be argued that such measures as the administration of oxygen are at the best only palliative, and of no use, since they do not remove the cause of the pathological conditions. As a physiologist I cannot agree with this reasoning. The living body is no machine, but constantly tending to maintain or to revert to the normal, and the respite afforded by such measures as the temporary administration of oxygen is not wasted but utilized for recuperation." It is pleasant to read such belief in the *vis medicatrix naturæ* from such an authority. Meltzer thinks that many patients have the power of storing oxygen in their tissues. This is not, I believe, accepted by physiologists, but the fact remains that the improvement after oxygen insufflation is usually very persistent.

In conclusion, it may be urged that oxygen should be employed in all serious cases of anoxemia and that its administration should not be delayed and only used as a *dernier ressort*, but should be employed early, before the vital tissues have been much damaged by the want of oxygen.

Conclusions. 1. Oxygen is of value whenever a state of anoxemia exists. This is universally recognized in cases of mountain sickness and sickness from high flying, and in poisoning by CO, nitrites and arseniuretted hydrogen and also in the effects of enemy gas.

2. For the same reasons oxygen should be tried in all cases of cyanosis, and also in acute respiratory conditions, such as pneumonia, when anoxemia threatens.

3. The ordinary method of giving oxygen by holding a funnel connected with the oxygen cylinder near the face of the patient is practically useless.

4. A better method than this is to give the gas through a rubber tube inserted into one nostril, and this may be made more effectual if the opposite nostril be rhythmically compressed during inspiration, the mouth, of course, being kept closed.

[12] Jour. Am. Med. Assn., September 14, 1918, p. 880.

5. The oxygen chamber is a very effectual way of giving oxygen, especially in chronic cases, but it involves much expense and care.

6. An extremely useful and effectual appliance for the administration of oxygen is Meltzer's apparatus for oral insufflation.

NOTE. — In the *British Medical Journal* March 6, 1920, Dr. J. C. Meakins shows that the arterial blood of the normal individual is nearly 5 per cent. "undersaturated" with oxygen, while in pneumonia the "undersaturation" may amount to nearly 18 per cent. By giving oxygen with the Haldane apparatus he was able to reduce the degree of undersaturation in the normal by one-half and in the pneumonic individual to just over 3 per cent. In other words, by the use of the method he increased the oxygen content of the blood of the cyanosed pneumonic person to above that of the normal individual. No better evidence than this could be needed of the value of oxygen inhalation in anoxemia.

A CASE OF SPLENOMEGALY WITH POLYMORPHONUCLEAR NEUTROPHIL HYPERLEUKOCYTOSIS.

BY E. L. TUOHY, B.A., M.D.,
DULUTH, MINN.

IN the November number, 1919, of this JOURNAL, p. 618, Dr. H. Z. Giffin, of the Mayo Clinic, presented a case of "Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly." As soon as this article appeared I immediately recalled a patient we had treated with curiously corresponding findings: a very large spleen; a very high leukocyte count markedly increasing after splenectomy; a gradual decrease in number thereafter, with marked constitutional improvement. Comparing the two cases the most striking difference appeared in the type of the leukocytes: Giffen's case presented marked and persistent eosinophilia; in our case there was an overwhelming preponderance of mature polymorphonuclear neutrophils. It is suggested to the reader that Giffin's article be reviewed in order to compare the two reports. His thorough search of the literature dealt largely with eosinophil leukocyte increase. It is notable, however, that he found in a thorough search of the literature little at all comparable with his case. I wish to present the following data, acknowledging that I have not consulted the Surgeon-General's Library nor made a thorough review of the literature; but that portion immediately available has shown nothing corresponding whatever except Giffin's report.

CASE HISTORY.—C. D., aged fifty-eight years; female; married; two daughters living and well. She was first seen November 21, 1917.

Family History. Negative.

Past History. Stated that she had acute arthritis at sixteen, but nothing eventful thereafter until signs of the menopause developed at forty, when she discovered she had uterine prolapse.

Present Complaint. On May 3, 1917, she developed severe pain in the left side. The physician who was called stated he found a large spleen. She was in bed four days and thought she had fever. The pain recurred at intervals, and each time she thought fever recurred. Four days before coming to the office she found difficulty in lying down or stooping or making any considerable movement of the body; cough or deep breathing gave much distress. She had lost twenty pounds in weight since the onset of this complaint, but had been up and around doing her work much of the time.

Physical Findings. Patient looks thin, tired and in evident distress. A very large tumor was found in the upper left quadrant, extending diagonally downward and toward the right, three inches beyond the navel and having the general characteristics of an enlarged spleen. It was very tender to pressure and the pain increased on movement. No spleen notch could be identified. General examination of the chest was negative. The fluoroscope showed some fixation of the left side of the diaphragm. It also showed the stomach crowded over to the right; the colon was not studied. Pelvic examination uncovered a pessary which she had worn for fourteen years. When this was removed the cervical area looked very angry, and it left some bleeding. Retroperitoneal septic accumulation was thought of, but the temperature was normal and nothing else corroborated such a hypothesis. Furthermore, after three days in the hospital, with vaginal douches, the local condition entirely cleared up. The blood showed a picture strikingly different than might have been expected from a splenomyelogenous leukemia. The first leukocyte count showed 65,000. The blood smears showed an overwhelming predominance of well-formed adult type polymorphonuclear neutrophil cells. After three days' rest in bed and symptomatic treatment the second leukocyte count showed 45,000.

Photomicrographs (Figs. 1 to 3), with lower, medium and higher magnification, show strikingly well the form of the leukocytes. The neutrophil granules took on the customary stain with Wright's stain, but the eosinophils were difficult to find, as were also the small lymphocytes. An average differential count showed: Polymorphonuclears, 99 per cent.; large lymphocytes, 0.5 per cent.; eosinophils, 0.5 per cent.; an occasional normoblast; 200 cells were counted. This relationship continued in all the differential counts made. Red-blood count showed 4,200,000 and hemoglobin 80 per cent. when the patient was first seen.

After continuing, with much discomfort and abdominal distress, operation was advised and carried out by Dr. W. A. Coventry, of this clinic, on December 3, 1917:

"A large spleen was found, strongly adherent to the diaphragm above and separated from the stomach wall with great diffi-

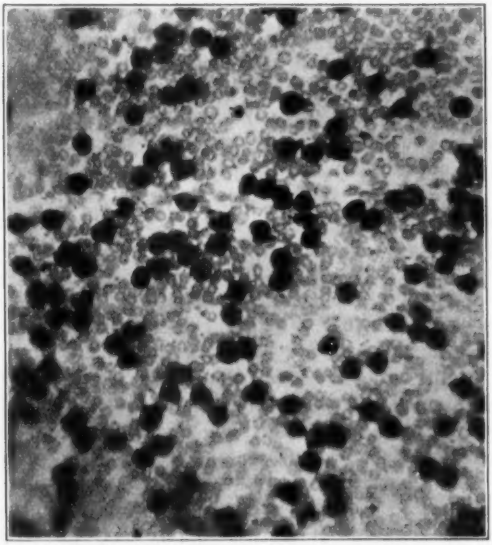

FIG. 1.—Photomicrograph of blood smear, showing the very large number of leukocytes in proportion to the red blood cells.

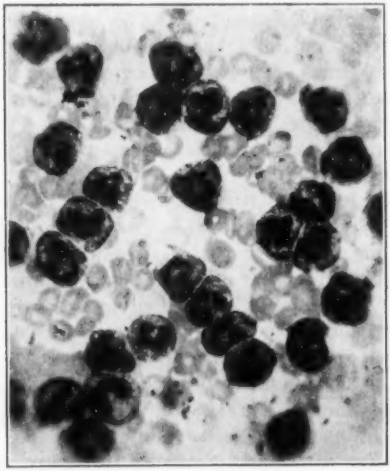

FIG. 2.—Photomicrograph with higher magnification, showing very well the nuclear structure and giving a suggestive outline of the granules.

culty. Sutures had to be placed in the outer wall of the stomach to close a possible defect. A decided perisplenitis accounted for these adhesions, particularly above and behind. The operation resulted in considerable shock so intravenous saline and other methods of stimulation were resorted to. After the second day recovery was uneventful except for some slight wound drainage, beginning after the sixth day and lasting for a week."

A decided increase in the leukocytes followed almost immediately after the operation. On December 6, 1917, the count was 240,000; on December 8 it was 175,000. This increase of about sixfold, while large, is not so greatly out of proportion as might

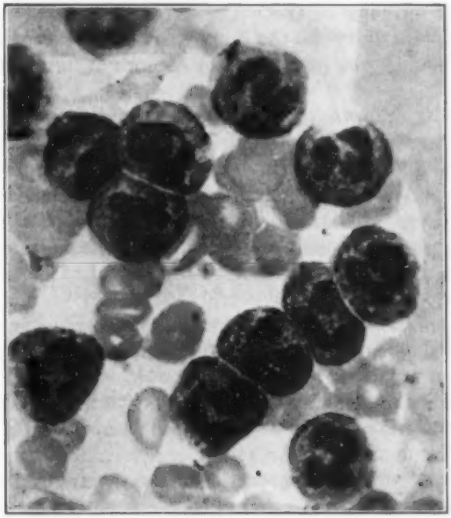

FIG. 3.—Photomicrograph with still higher magnifications and beautifully showing the adult type of well-formed nuclei and also showing granules.

appear, since splenectomy or even hysterectomy has been known to transiently increase a low count to a similar degree. The count on December 12 was 50,000; at the time of leaving the hospital, December 29, the count was 45,000. She was able to walk around easily, had lost much of her nervousness and was eating well.

She went away some distance to her home. We had no opportunity for further blood counts, but her daughter reported, from time to time, a rapid improvement in her health, increase in strength, and that she had again assumed her usual household duties.

When she was again seen it was by one of my associates, and at a time when we were having the epidemic of streptococcus lung infection that occurred in the spring of 1918. She entered the

hospital on April 27, 1918, in a comatose condition. She had then been sick about one week. Massive dulness was reported over the bases of both lungs, more on the left than on the right. She was raising bloody, frothy material and died within two hours. An autopsy was not permitted and her sudden death made procrastination in getting blood smears particularly unfortunate.

Discussion. The data in this case are lacking in many points of interest. The persistent increase, however, in adult polymorphonuclear leukocytes, associated with splenomegaly was so definite as to merit an analysis of the factors concerned. It requires courage to plunge into any discussion involving the spleen; in so doing we are easily led into a consideration of controversial matter. However, certain light seems to be thrown on the spleen function in the presence of hyperactivity in the bone-marrow yielding an excessive number of leukocytes (even though of normal forms) in the circulating blood.

In the embryo, up to the fourth month of fetal life, both the spleen and bone-marrow form red blood cells; both, together with certain lymph gland and lymph-adenoid tissue, possibly also the liver, form myeloblasts. After the fourth month of fetal life both erythroblasts and myeloblasts are formed almost entirely in the bone-marrow. Thereafter, physiologically and pathologically, we may state that the bone-marrow and the spleen, *in the process of blood regeneration and destruction, work coördinately.*

The normal disposition of incapacitated red blood cells seems to be accomplished largely through the filtration or sieve-like action of the spleen pulp, the discarded material being carted to the liver and becoming the ultimate source of pigment in the bile. Obsolete polymorphonuclear leukocytes seem to meet a similar fate, although probably a large number, particularly when called forth by localized inflammation or other chemotactic influences, are cast off from the body in the form of discharges, such as is seen in purulent sputum, discharging abscess or in pyelocystitis producing pyuria. But when we know that the bone-marrow is hyperfunctioning for considerable periods of time without known avenues of escape for either the excess of red or white cells it seems logical to assume there will be an overfunction of the spleen, with enlargement. Incidentally, we may remark that much more is known concerning the general method of erythrocyte destruction and replacement than of the similar process obtaining for leukocytes.

A consideration of certain well-known pathological entities illustrates well the position taken by the spleen and further demonstrates its response to varying degrees of activity in the bone-marrow. This must be considered for the time being totally regardless of the ultimate etiological factors controlling hematopoietic function:

1. We do not find spleen enlargement in the presence of a severe secondary anemia, for example, that caused by carcinoma of the stomach, with gradual enteric bleeding.

2. In the severest types of fulminating pernicious anemia (aplastic), with fatigued, overtaxed and hypoplastic bone-marrow, we have no spleen or liver enlargement.

3. It is difficult with our present knowledge to speak dogmatically concerning the constancy of spleen hyperfunction in so-called idiopathic pernicious anemia. However, with the H–H index,[1] over one and higher, as elicited by a determination of pigment values in the duodenal contents, and with a patient showing an icteric tendency, spleen enlargement is usually demonstrable.

4. In Vaquez's disease splenomegaly is one of the triad of symptoms upon which the diagnosis is made; the liver is choked with blood-derived pigment.

5. In the anemia of hemolytic icterus, whether familial or acquired, the results of hyperactivity in the bone-marrow are lost through the hyperfunctioning of the enlarged spleen; dramatically enough the disease is cured by splenectomy. This is true whether the inherent stimulus to overdestruction resides in the spleen itself or whether that organ is the unwitting agent of some extraneous factor.

6. The same principle holds with that group of anemias loosely classified as "splenic anemia." When localized spleen disease, notably syphilis or tuberculosis, has been proved, persistent and extreme secondary anemias have been promptly ameliorated by splenectomy.

The inference is left by W. J. Mayo, in an excellent article developing the surgical indications for splenectomy,[2] that the remaining anemias in this group, however named, represent similar splenic processes as yet unknown and unidentified. The abdominal conditions associated with cirrhosis of the liver are similarly given plausible consideration and the splenic factor in visceral circulation analyzed.

7. There is a conversational opinion expressed occasionally by men of experience that myeloid leukemia or myelocythemia represents a malignant overproduction of the bone-marrow, resulting in primitive cell forms, sarcomatous in nature, flooding the circulation. It is true that when this disease is well developed the whole hematopoietic system is involved. Then it is that leukemic tumors may be found in almost any tissue, definitely metastasizing. The much enlarged spleen led to the earlier conclusion that these metastatic agglomerations therein became the source of many of the forms in the blood. The early course of the disease, nevertheless, points strikingly to the attempt on the part of the spleen to exercise the basic function of the pulp spaces to keep these abnormal elements out of the blood, for the same reason as they engulf the broken-down and damaged erythrocytes in malaria. Hence it is that the Mal-

[1] Schneider, J. P.: Further Quantitative Study of Duodenal Blood-derived Pigments, Arch. Int. Med., 1917.

[2] Mayo, W. J.: Ann. Surg., July, 1919.

pighian corpuscles are pushed aside and the pulp spaces become clogged with masses of myeloblastic elements. As further supporting this screen function of the spleen we have:

(*a*) In the few cases of myeloid leukemia in which splenectomy has been performed the accessory spleens and lymph gland tissues have undergone hyperplasia.

(*b*) In following the direct vascular connection beween the spleen pulp and the liver (well illustrated by pigment deposition in the liver in active pernicious anemia) we see the reason for the earliest, exquisite evidence of invasion of the general tissues in myeloid leukemia (just as in lymph-gland enlargement in the drainage area of the breast in carcinoma the glands withstand the brunt of the invasion, until they are overwhelmed).

There is, therefore, striking argument in support of the general assumption that the spleen exercises physically and pathologically a filtering or screen capacity. At operation in this case there was no indication of liver involvement or glandular enlargement; in other words, nothing to indicate that the spleen was overrun or overpowered. This case, even more than Giffin's, would seem to indicate that under certain conditions there can be a calling forth of particular types of leukocytes, normal in form and structure, without any apparent tendency to ultimate failure on the part of the bone-marrow (as shown by a mobilization of embryonal or immature forms), seeming to exemplify the ability of the bone-marrow to hyperfunction in a benign way. What the chemotactic irritant was in this case must remain unsolved. Splenomegaly, as might be expected, took place to a marked degree. It appears more likely that the massive adhesions about the spleen were the result of hyperactivity and congestion in that organ, with overgrowth of connective tissue rather than the inherent cause of the leukocytosis itself. The long-continued irritation due to the wearing of the pessary is only one possibility and the usual possibilities of focal infection come to mind. Indeed, the ultimate mechanism or device which stimulates or restrains the bone-marrow in its degrees of activity, depending on bodily needs, is poorly understood. It is known that different types of leukocytes appear in the blood under the influence of varying irritants or infections, such as eosinophilia in trichinosis and an increase in large lymphocytes in malaria or pertussis. But wherever this control may be found ultimately to lie it probably follows the rule of other physiological processes: a definite sequence of events transpiring whenever certain elemental stimuli are given recognition. This makes it possible for the ensuing circle of events to be broken in any portion of the chain and the disease picture that results must vary greatly, depending on the position and type of the break. The disturbance of one segment of the hematopoietic system yields lymphatic leukemia or Hodgkin's; overstimulation of the bone-marrow from as yet unknown sources

produces another picture. But whether the end-products of this hyperfunction, circulating in the blood produce the picture of hyperleukocytosis or a leukemia must depend on whether the myeloblastic production is lawful and benign, or Bolshevistic and malignant. In either case splenomegaly can be expected. *The spleen and bone-marrow hyperfunction coördinately.*

For H. Z. Giffin's kindly interest in this case and his opinion and studies of the blood slides as well as the making of the photomicrographs, I wish to acknowledge my deep indebtedness.

A COMPARATIVE STUDY OF THE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.

By Jay F. Schamberg, M.D., John A. Kolmer, M.D.,

and

George W. Raiziss, Ph.D.,

PHILADELPHIA.

(From the Dermatological Research Laboratories of Philadelphia.)

As the result of comparative therapeutic tests conducted by Hata[1] in hen spirillosis and with mice infected with S. obermayeri, Ehrlich announced that 0.9 gram neosalvarsan possesses the curative value of 0.6 gram salvarsan; from the practical standpoint of treatment in syphilis this subject is of great importance, and particularly so by reason of the opinions held by several syphilographers of experience that neoarsphenamine in the amounts commonly administered (0.6 to 0.9 gram) does not appear to possess the same therapeutic activity as arsphenamine (0.4 to 0.6 gram).

Purpose of Investigation. In our experiments conducted for the purpose of ascertaining the comparative therapeutic activity of arsphenamine and neoarsphenamine, we utilized rats infected with a virulent strain of T. equiperdum, to ascertain the smallest amounts of arsphenamine and neoarsphenamine, produced by other laboratories and by ourselves, that would sterilize animals infected twenty-four hours before with intraperitoneal injections of approximately known numbers of trypanosomes. Inasmuch as the trypanosomes in the control animals appeared in the peripheral blood within forty-eight hours and caused death in from the fifth to seventh day, these experiments yielded quite sharp and definite results, although constituting a severe test of the therapeutic activity of the compounds.

A second purpose of these studies was to determine whether differ-

[1] The Experimental Chemotherapy of Spirilloses, Rebman, London, 1911.

ent lots of arsphenamine and neoarsphenamine showed variation in their trypanocidal activity, in the same manner that their toxicity is likely to vary;[2] this is likewise a subject of much practical importance from the standpoint of standardization of these compounds.

Practical Value of Trypanocidal Tests for Determining the Curative Properties of Arsphenamine and Neoarsphenamine. From the standpoint of treatment of syphilis, therapeutic tests employing rabbits infected with T. pallidum are in some respects to be preferred, but rabbits vary considerably in susceptibility to testicular and generalized infections, tend to recover spontaneously, the Treponema is very susceptible to the influence of arsenical compounds, and is not well adapted for experiments designed to elicit sharp differences in therapeutic activity; furthermore, thorough examinations of the lesions for evidences of therapeutic effects are very laborious and time consuming. In addition very large numbers of rabbits are required for testing a few compounds, adding greatly to the expense and labor involved.

Trypanocidal tests, however, utilize a smaller and cheaper animal, infections are regular and sure, the evidences of therapeutic activity insofar as arsphenamine and neoarsphenamine are concerned are sharp and decisive, and not more than two or three weeks of observation are required for the results.

Insofar as comparative therapeutic tests with arsphenamine and neoarsphenamine are concerned we believe that trypanocidal tests may be accepted as an index of therapeutic activity because both compounds are markedly trypanocidal, the value of these tests is, however, sharply limited inasmuch as certain other medicinals of value in the treatment of pallida infections, notably the mercurials,[3] are unable to influence the course of experimental trypanosomiasis, due in part to their high toxicity which thereby prevents the administration of sufficiently large doses; *trypanocidal tests may be regarded therefore as possessing a positive value only,* that is, they may be taken as a method of determining comparative therapeutic activity of medicinals possessing trypanocidal activity *in vivo;* medicinals such as the mercurials which fail to influence trypanosomiasis of animals, may still possess spirocheticidal properties and for this reason *negative trypanocidal tests are of little or no value in excluding the therapeutic activity of these compounds in syphilis.*

We are not aware of any evidence that tends to invalidate the proposition that arsphenamine and neoarsphenamine proving trypanocidal *in vivo* will exert spirocheticidal properties *in vivo* and prove therapeutically active in syphilis; as stated above, how-

[2] Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: Comparative Studies of the Toxicity of Arsphenamine and Neoarsphenamine, Am. Jour. Med. Sc. (To be published later).

[3] Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: The Chemotherapy of Mercurial Compounds, Am. Jour. Syph., 1917, i, 1–43.

ever, the converse is not necessarily true, that is, medicinals as the mercurials, failing to influence trypanosomiasis will not necessarily fail to influence infections with T. pallidum.

As stated by Pearce and Brown[4] the treatment of experimental trypanosomiasis of mice and rats is largely a matter of speed of action yielding valuable data in a relatively short space of time on the therapeutic activity of a compound. These investigators, however, have very properly stated that experiments of this character do not involve the treatment of chronic tissue changes as in trypanosomiasis of guinea-pigs and rabbits, which are more nearly analogous to the naturally acquired forms of the disease, but that the two types of infections supplement each other in the chemotherapy of experimental trypanosomiasis.

Technic of Trypanocidal Tests. The strain of T. equiperdum employed in our experiments appears in the peripheral blood (tail) within forty-eight to seventy-two hours after intraperitoneal infection; by the fifth to seventh days after infections enormous numbers of trypanosomes are in the blood and may outnumber the erythrocytes. The animals usually die on the fifth to seventh days. We have found the results with this strain to be sharper and more decisive than those observed with the relatively non-virulent T. lewisi and better than with T. brucei, which is usually too virulent and kills too quickly.

Rats weighing from 100 to 150 gm. are employed; pregnant animals are excluded. Each animal is weighed after eighteen hours' fasting and injected with a dose of arsphenamine or neoarsphenamine according to body weight. (See Table I.)

The question of infection is very important in relation to the results of these tests; we routinely infect twenty-four hours before administering the medicinal, the infection having this much headway before treatment begins. The number of trypanosomes used in infecting the animals greatly influences the results as shown in a previous paper by Kolmer;[5] infection with a great number of trypanosomes requires a much larger dose of arsphenamine or neoarsphenamine for sterilization than infection with a small number, and the method proposed for counting the trypanosomes and infecting with approximately known numbers with blood removed aseptically from the heart of the seed animal[6] has proved of distinct value. It is only by using rats of approximately the same weight and infecting with approximately known numbers of trypanosomes by intraperitoneal injection that the experiments are rendered uniform

[4] Experimental Trypanosomiasis: its Applications in Chemotherapeutic Investigations, Jour. Exper. Med., 1918, xxviii, 109–147.

[5] A Method of Transmitting Known Numbers of Trypanosomes, with a Note on the Numeric Relationship of Trypanosomiasis to Infection, Jour. Infect. Dis., 1915, xvii, 79–94.

[6] Kolmer, J. A.: A Method of Transmitting Blood Parasites, Jour. Infect. Dis., 1915, xvi, 311–312.

TABLE I.—THE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.*

No.	Wt., gm.	Sex.	Compound.	Dose per kilo.	Results in days after treatment.											
					1	2	3	4	5	6	7	8	9	10	11	12
1	145	F.		0.010	–	–	–	–	–	–	–	Few	++	++++	++++	D.
2	130	M.		0.015	–	–	–	–	–	–	–	–	Few	+++	++++	++++
3	150	F.	Neoarsphen.	0.020	–	–	–	–	–	–	–	–	–	–	–	–†
4	160	F.	(Lab. No. 2)	0.030	–	–	–	–	–	–	–	–	–	–	–	–
5	140	M.		0.040	–	–	–	–	–	–	–	–	–	–	–	–
6	145	F.		0.010	–	–	Few	++	++++	++++	++++	D.				
7	160	F.		0.015	–	–	–	–	–	Few	+	+++	++++	++++	D.	
8	130	M.	Neoarsphen.	0.020	–	–	–	–	–	Few	++	+++	++++	++++	D.	
9	170	M.	(Lab. No. 2)	0.030	–	–	–	–	–	–	–	–	–	+	++	++++
10	170	F.		0.040	–	–	–	–	–	–	–	–	–	–	–	–
11	145	F.		0.005	–	–	–	–	–	–	–	Few	+	+++	++++	D.
12	115	F.		0.008	–	–	–	–	–	–	–	Few	++	+++	++++	++++
13	210	M.	Arsphen.	0.010	–	–	–	–	–	–	–	–	–	Few	++	+++
14	180	F.	(Lab. No. 2)	0.015	–	–	–	–	–	–	–	–	–	–	Few	++
15	150	F.		0.020	–	–	–	–	–	–	–	–	–	–	–	–
16	170	M.		0	–	Few	+	++++	++++	++++	D.					
17	165	F.	Controls	0	–	Few	Few	++	+++	++++	D.					
18	215	M.		0	–	Few	+++	++++	++++	++++	D.					
19	140	F.		0	–	–	Few	++	++++	++++	++++	D.				

* Rats infected twenty-four hours previously with intraperitoneal injections of 231,000 T. equiperdum.
† This rat developed trypanosomiasis on the sixteenth day and died on the nineteenth day.

and comparative;[7] additional experiments by Kolmer and Yagel[8] have emphasized the importance of these factors in the technic, and have shown that when the animals vary greatly in weight, best results are secured by infecting with trypanosomes according to the weight of each animal. With rats weighing from 100 to 200 gm. uniform infections are secured with 250,000 to 500,000 trypanosomes per rat; lighter infections suffice and render the results more delicate as shown in Table II, but under these conditions one or more of the controls may not develop trypanosomiasis and thereby cloud the interpretation of the entire experiment.

TABLE II.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.*

Compound.	Dose per kilo.	Results in days after treatment.						
		1	2	3	4	5	6	7
Arsphenamine (Lab. No. 2)	0.008	–	–	–	–	–	–	–
	0.010	–	–	–	–	–	–	–
	0.020	–	–	–	–	–	–	–
	0.030	–	–	–	–	–	–	–
Neoarsphenamine (Lab. No. 2)	0.010	–	–	–	–	–	–	–
	0.020	–	–	–	–	–	–	–
	0.030	–	–	–	–	–	–	–
	0.040	–	–	–	–	–	–	–
Neoarsphenamine (Lab. No. 2)	0.010	–	–	–	Few	+	++++	D.
	0.020	–	–	–	–	–	Few	++++
	0.030	–	–	–	–	–	–	–
	0.040	–	–	–	–	–	–	–
Neoarsphenamine (Lab. No. 2)	0.010	–	–	–	Few	+	++++	D
	0.020	–	–	–	–	–	Few	++++
	0.030	–	–	–	–	–	–	–
	0.040	–	–	–	–	–	–	–
Controls . . .	None	–	–	–	Few	+	+++	D.
	None	–	–	–	Few	+	++++	D.

* Rats infected with 180,000 T. equiperdum.

The dose of arsphenamine and neoarsphenamine is prepared separately for each rat in small sterile vials and is contained in 1 c.c. which is slowly injected with a syringe in a saphenous vein; in testing arsphenamine doses ranging from 0.005 to 0.020 gm. per kilogram of rat were generally administered and neoarsphenamine in doses ranging from 0.008 to 0.040 gm. per kilo.

The blood of each animal, including the controls, is examined each day over a period of three weeks by placing a drop from the tail on a cover-glass and allowing the blood to spread in a film when placed upon a slide; the results are recorded numerically as few,

[7] Kolmer, J. A., Schamberg, J. F., and Raiziss, G. W.: The Numeric Relationship of Infection to the Chemotherapy of Experimental Trypanosomiasis, Jour. Infect. Dis., 1917, xx, 35–44.

[8] A Further Study of the Numerical Relationship of Infection to Experimental Trypanosomiasis and Influence upon Chemotherapeutic Tests. (To be published.)

TABLE III.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.*

Compound.	Dose per kilo.	Results in days after treatment.							
		1	2	3	4	5	6	7	8
Neoarsphenamine (Lab. No. 2)	0.010	....	.....	+	+++	++++	D.		
	0.020	–	–	–	–	–	–	–	–
	0.030	–	–	– –	–	–	–	–	–†
	0.040	–	–	–	–	–	–	–	–†
Neoarsphenamine (Lab. No. 5)	0.010	–	+	+++	++++	D.			
	0.020	–	–	–	–	–	–	Few	++
	0.030	–	–	–	–	–	–	–	–
	0.040	–		–	–	–	–	–	–†
Neoarsphenamine (Lab. No. 3)	0.010	....	....	....	..	....	Few	+++	++++
	0.020		–	–	–	–	–	–	–
	0.030	–	–	–	–	–	–	–	–†
	0.040	–	–	–	–	–	–	–	–†
Neoarsphenamine (Lab. No. 6)	0.010	–	–	–	–	–	Few	++	++++
	0.020	–	–	–	–	–	–	–	–†
	0.030	–	–	–	–	–	–	–	–
	0.040	–	–	–	–	–	–	–	–†
Neoarsphenamine (Lab. No. 2)	0.010	–	–	Few	++	++++	++++	D.	
	0.020	–	–	–	–	–	Few	+	++
	0.030	–	–	–	–	–	–	–	–†
	0.040	–	–	–			–	–	–
Arsphenamine (Lab. No. 1)	0.008	–	–	Few	+	++	++++	D.	
	0.010	–	–	–	–	–	–	Few	++
	0.020	–	–	–	–	–	–	–	–
	0.030	–	–	–	–	–	–	–	–
Controls	None	Few	+	++++	++++	D.			
	None	Few	+	++++	++++	D.			

* Rats infected with 500,000 T. equiperdum.
† These rats developed trypanosomiasis after the eighth day and died about five days later.

+, ++, +++ and ++++, the latter referring to the presence of numbers of trypanosomes too numerous to be counted.

TABLE IV.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.*

Compound.	Dose per kilo.	Results in days after treatment.						
		1	2	3	4	5	6	7
Arsphenamine (Lab. No. 2)	0.008	−	+	+++	D.			
	0.010	−	−	−	−	−	−	−
	0.020	−	−	−	−	−	−	−
	0.030	−	−	−	−	−	−	−
Neoarsphenamine (Lab. No. 2)	0.010	Few	+	++++	D.			
	0.020	−	−	−	−	−	−	−
	0.030	−	−	−	−	−	−	−
	0.040	−	−	−	−	−	−	−
Neoarsphenamine (Lab. No. 4)	0.010	Few	++	++++	D.			
	0.020	−	Few	++++	D.			
	0.030	−	−	−	−	−	−	−†
	0.040	−	−	−	−	−	−	−
Controls	None	Few	++++	++++	D.			
	None	−	+	++++	++++	D.		
	None	Few	++++	++++	D.			
	None	−	+	++++	++++	D.		

* Rats infected with 600,000 T. equiperdum.
† This rat developed trypanosomiasis on eighth day and died on twelfth day.

TABLE V.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.*

Compound.	Dose per kilo.	Results in days after treatment.						
		1	2	3	4	5	6	7
Arsphen. (Lab. No. 2)	0.030	−	−	−	−	−	−	−
	0.020	−	−	−	−	−	−	−
	0.010	−	−	−	−	−	+	+++
	0.008	−	−	−	Few	+	+++	D.
	0.005	−	−	−	−	D.		
	0.003	−	Few	+	++	+++	++++	D.
Neoarsphen. (Lab. No. 2)	0.040	−	−	−	−	−	−	−
	0.030	−	−	−	−	−	−	−
	0.020	−	−	−	−	−	−	−†
	0.010	−	−	−	+	++++	++++	D.
	0.008	−	−	+	++	++++	D.	
	0.005	−	Few	++++	D.			
Controls	None	+	++++	D.				
	None	Few	+++	++++	D.			
	None	Few	+++	++++	++++	D.		
	None	+	+++	++++	++++	D.		

* Rats infected with 500,000 T. equiperdum.
† Developed trypanosomiasis on eighth day; died on fourteenth day.

A twenty-one-day period of observation is necessary, inasmuch as trypanosomes may appear in the peripheral blood of animals

TABLE VI.—COMPARATIVE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE AND NEOARSPHENAMINE.*

Compound.	Dose per kilo.	Results in days after treatment.							
		1	2	3	4	5	6	7	8
Neoarsphenamine (Lab. No. 2)	0.008	–	–	–	–	Few	++	++++	D.
	0.008	–	–	Few	+	++	++++	D.	
	0.010	–	–	–	Few	+	++++	++++	D.
	0.010	–	–	–	Few	+	+++	++++	++++
	0.020	–	–	–	–	–	–	–	Few
	0.020	–	–	–	–	–	–	–	–†
	0.030	–	–	–	–	–	–	–	–
	0.030	–	–	–	–	–	–	–	–
Arsphenamine (Lab. No. 2)	0.003	–	Few	+	++	+++	++++	D.	
	0.003	–	Few	+	++	++++	D.		
	0.008	–	–	–	Few	+	++++	++++	D.
	0.008	–	–	–	Few	+	++++	D.	
	0.010	–	–	–	–	–	Few	+	++
	0.010	–	–	–	–	Few	+	+++	++++
	0.020	–	–	–	–	–	–	–	–
	0.020	–	–	–	–	–	–	–	–
Controls	None	Few	++	++++	D.				
	None	Few	+++	++++	++++	D.			

* Rats infected with 500,000 T. equiperdum.
† Rat developed trypanosomiasis on the eleventh day and died on the fourteenth.

treated with arsphenamine and neoarsphenamine as late as sixteen days after infection; all rats proving sterile at the end of three weeks usually live indefinitely insofar as the effects of the experiment are concerned. The examination for trypanosomes in the tail blood begins on the day following treatment which is the third day after infection; the results are recorded in this manner. (See Tables I to VI.) As is usual in tests of this kind the results are never mathematically accurate and rats frequently die without showing trypanosomes in their blood.

TABLE VII.—THE TRYPANOCIDAL ACTIVITY OF ARSPHENAMINE PREPARED BY DIFFERENT LABORATORIES.

Compounds.	Smallest sterilizing doses per kilogram of weight.									Average.
	Exper. 1.	Exper. 2.	Exper. 3.	Exper. 4.	Exper. 5.	Exper. 6.	Exper. 7.	Exper. 8.	Exper. 9.	
Lab. No. 1 . .	0.02	0.02	..	..	..	..	..	..	..	0.0200
Lab. No. 2 . .	0.02	0.03	0.02	0.02	0.02	0.01	0.015	0.02	0.015	0.0188
Lab. No. 3 . .	0.03	0.02	..	..	..	..	..	..	..	0.0250
Lab. No. 4 . .	0.03	0.03	0.02	..	..	..	..	..	..	0.0260
Lab. No. 5 . .	0.02	0.03	0.02	..	..	..	..	..	..	0.0230
Lab. No. 6 . .	0.02	0.03	..	..	..	..	..	..	..	0.0250

TABLE VIII.—THE TRYPANOCIDAL ACTIVITY OF NEOARSPHENAMINE PREPARED BY DIFFERENT LABORATORIES.

Compounds.	Smallest sterilizing doses per kilogram of weight.							Average.
	Exper. 1.	Exper. 2.	Exper. 3.	Exper. 4.	Exper. 5.	Exper. 6.	Exper. 7.	
Lab. No. 1	0.04	0.02	More than 0.04	0.03	..	..	..	0.043+
Lab. No. 2	0.04	0.03	0.03	0.04	More than 0.04	0.02	0.03	0.033+
Lab. No. 3	0.03	0.02	More than 0.04	..	..	..	..	0.030+
Lab. No. 4	0.04	More than 0.04	..	..	..	..	..	0.040+
Lab. No. 5	0.03	0.02	0.04	More than 0.04	..	..	..	0.033+
Lab. No. 6	0.04	0.04	..	..	..	..	..	0.040

Results. The results of a number of experiments with arsphenamine and neoarsphenamine prepared by six different laboratories are shown in Tables I to VI as examples; a summary of these tests

is presented in Tables VII and VIII giving the smallest amounts of each compound per kilogram of rat, proving sufficient for sterilization of the animal, as determined by a period of three weeks of observation.

Summary. 1. The smallest trypanocidal doses of arsphenamine (*for the strain used in our experiments*) ranged from 0.010 to 0.030 gm. per kilogram of body weight of rat; the average for the arsphenamines of the six different laboratories ranged from 0.0188 to 0.026 gm. per kilogram of weight, giving a general average based upon tests conducted with twenty-one compounds, of about 0.023 gm. per kilogram of weight as the trypanocidal dose.

2. The smallest trypanocidal doses of neoarsphenamine ranged from 0.020 to more than 0.040 gm. per kilogram of body weight; the average for the neoarsphenamines of the six different laboratories ranged from 0.030 to more than 0.043 gm. per kilogram of rat, giving a general average based upon tests conducted with twenty-two compounds, of from 0.037 to 0.040 gm. per kilogram of weight, as the trypanocidal dose.

3. According to these tests arsphenamine is about 1.7 times as trypanocidal as neoarsphenamine, the ratio being:

$$\frac{\text{Smallest trypanocidal dose of arsphenamine, 0.023 gram}}{\text{Smallest trypanocidal dose of neoarsphenamine, 0.04 gram}} = 1.74$$

According to Castelli's[9] [10] report (see Table IX) the following ratios may be made out for other microparasites:

$$\frac{\text{Smallest dose of arsphenamine for S. obermayer, 0.10656 gram}}{\text{Smallest dose of neoarsphenamine for S. obermayer, 0.1998 gram}} = 1.78$$

$$\frac{\text{Smallest dose of arsphenamine for hen spirillosis, 0.0035 gram}}{\text{Smallest dose of neoarsphenamine for hen spirillosis, 0.006 gram}} = 1.7$$

$$\frac{\text{Smallest dose of arsphenamine for rabbit syphilis, 0.0235 gram}}{\text{Smallest dose of neoarsphenamine for rabbit syphilis, 0.035 gram}} = 1.5$$

TABLE IX.—THERAPEUTIC DOSES OF SALVARSAN AND NEOSALVARSAN AS GIVEN BY CASTELLI.

Animal.	Infection.	Route of administration.	Sterilizing doses per kilo.	
			Salvarsan.	Neosalvarsan.
Mouse	Recurrent fever	Subcutaneous	0.10656	0.1665
Mouse	Recurrent fever	Intravenous	0.10656	0.1998
Hen	Spirillosis	Intramuscular	0.00350	0.0060
Rabbit	Syphilis	Intravenous	0.02–0.027	0.03–0.04*

* Doses killing spirochetes in testicular lesions in twenty-four hours.

[9] Castelli, G.: Ueber Neosalvarsan. Bestimmung der Toxizität und der heilenden Wirkung bei experimentellen Spirochätenkrankheiten, Ztschr. f. chemotherapie orig., 1912–1913, i, 321–352.

[10] Castelli, G.: Ueber Neosalvarsan, Ztschr. f. chemotherapie, orig., 1912–1913, i, 122–135.

Our results are therefore in close agreement with those of Castelli and indicate that arsphenamine is from 1.5 to almost 1.8 times more active therapeutically against virulent trypanosomes, spirilla and T. pallida than neoarsphenamine; it is also of interest to note in this connection the close parallelism among the ratios for the different microparasites employed in these tests by Castelli and ourselves.

4. According to these results Ehrlich's ratio of therapeutic activity given as 0.6 gm. arsphenamine equal to 0.9 gm. neoarsphenamine is incorrect; rather 0.6 gm. arsphenamine is equal to about 1.05 gm. neoarsphenamine. In the treatment of syphilis with neoarsphenamine either larger doses are indicated than are usually given or probably better still, the same or smaller doses at more frequent intervals.

5. The ratio of *dosis therapeutica* to *dosis tolerata* of the two compounds is very interesting and may be stated as follows:

(*a*) The trypanocidal dose (dosis therapeutica) of arsphenamine is 4.56 times less the highest tolerated dose (dosis tolerata) according to the ratio:

$$\frac{\text{Dosis tolerata, 0.105 gram per kilo}}{\text{Dosis therapeutica, 0.023 gram per kilo}} = 4.56$$

(*b*) The trypanocidal dose of neoarsphenamine is 6.35 times less the highest tolerated dose according to the ratio:

$$\frac{\text{Dosis tolerata, 0.254 gram per kilo}}{\text{Dosis therapeutica, 0.04 gram per kilo}} = 6.35$$

From these results it is evident that neoarsphenamine is a safer drug; even when doses of 1 gm. of neoarsphenamine which approximates 0.6 gm. of arsphenamine in therapeutic activity are given in the treatment of syphilis there remains a larger margin of safety.

Conclusions. 1. Trypanocidal tests employing rats infected with T. equiperdum provide a means for determining the curative properties of arsphenamine and neoarsphenamine.

2. Such medicinals as arsphenamine and neoarsphenamine proving trypanocidal *in vivo* are probably curative in syphilis; other compounds as the mercurials, which are unable to influence experimental trypanosomiasis, may still influence infections with T. pallida; trypanocidal tests possess, therefore, a greater positive than negative value in chemotherapeutic studies in syphilis.

3. In conducting trypanocidal tests the virulence of the strain, the method of infection, the interval between infection and treatment and the weight of the test animals are modifying factors and must be rendered uniform to secure satisfactory results.

4. With the strain of T. equiperdum employed in these experiments the smallest amounts of arsphenamine sterilizing rats infected

twenty-four hours previously varied from 0.010 to 0.030 gm. per kilo of body weight, the general average for twenty-one compounds prepared by six different laboratories, being 0.023 gm. per kilo of rat.

5. The smallest sterilizing doses of neoarsphenamine under identical conditions varied from 0.020 gm. to more than 0.040 gm. per kilo of rat; the general average for twenty-two compounds from six different laboratories was about 0.040 gm. per kilo.

6. The trypanocidal activity of different lots of arsphenamine and neoarsphenamine prepared by the same laboratory and by different laboratories varied in a manner analogous to variations in lethal toxicity for rats.

7. The trypanocidal activity of arsphenamine is 1.74 times greater than that of neoarsphenamine; in experimental infections with S. obermayeri, hen spirillosis and rabbit syphilis, Castelli found arsphenamine from 1.5 to 1.78 times more active therapeutically than neoarsphenamine.

8. According to these results 0.6 gm. arsphenamine equals 1.05 rather than 0.9 gm. of neoarsphenamine in therapeutic activity.

9. The trypanocidal dose (dosis therapeutica) of arsphenamine is 4.56 times less the highest tolerated dose for the rat (dosis tolerata); the trypanocidal dose of neoarsphenamine is 6.35 times less the highest tolerated dose.

10. These results indicate that neoarsphenamine is a somewhat safer compound than arsphenamine; even when 1 gm. of neoarsphenamine is administered as equivalent in therapeutic activity to 0.6 gm. arsphenamine, the margin of safety is greater.

CONTRACTION WAVES IN THE NORMAL AND HYDRONEPHROTIC URETER: AN EXPERIMENTAL STUDY.

By Wilder G. Penfield, B.A. (Oxon.), M.D.,
Oxford, England.

(From the Laboratory of Surgical Research, Harvard Medical School.)

Most of the extensive work that has been done on hydronephrosis has been confined to the kidneys. At the suggestion of Dr. W. C. Quinby the experiments reported here were undertaken to study the ureter in this condition.

Method. Rabbits were found to lend themselves readily to observation of the ureter *in situ*, while dogs were used both for this purpose and for the study of ureteral peristalsis *in vitro*. The method employed was briefly as follows:

Each animal was etherized. With strict aseptic precautions a small ventral incision was made in the abdomen and a rubber band of small caliber fastened about one ureter, just above the bladder, so as to cause a partial constriction. In a few cases this ligation was made higher up. The abdominal incision was then closed.

An incomplete ligation was preferred to a complete one for the following reasons: (*a*) The resultant hydronephrosis is of slower development but greater in degree.[1,2] (*b*) The condition would thus more nearly resemble clinical hydronephrosis which is usually caused by partial or recurring obstruction. (*c*) Only in one recorded experimental case has atrophy of the kidney followed incomplete ligation, whereas it almost always follows complete ligation.[3]

After a period varying from three weeks to five months a second operation was performed. The dogs were etherized a second time, the rabbits were anesthetized with paraldehyde. A long, ventral abdominal incision was now made, the rectum cut across at its lowest point and all of the intestines reflected upward after cutting the root of the mesentery as high as the superior mesenteric artery. This exposed both ureters to inspection throughout their course. The whole preparation was placed for observation under glass in a chamber maintained at a temperature of 38° C.

After observation *in vivo*, both the normal and hydronephrotic ureters were removed from the dog and placed in oxygenated Locke's solution* at 38° C. During the succeeding twelve hours experiments were performed on each ureter. Instead of excising separate strip or ring segments, as previous experimenters have done,[4,5,6,7,8] the whole ureter was preserved intact. A ring segment of about 1 cm. at either end of the ureter was caused to record its contractions by means of loops of fine silk passed on a needle† through the ureter wall and out at the end of the ureter. Thus a ring of circular muscle was included in the loops. These segments were connected in this way with light, balanced, writing levers which registered on a smoked drum. The beginning and the end of a wave of peristalsis, or retroperistalsis, was thus graphically recorded as well as the time required for the passage of the wave.

As a result of the first operation marked unilateral dilatation of the ureter and pelvis was found in every case but one, a series of thirty-two animals being used. In previous experiments on hydronephrosis atrophy of the ureter walls has been found in the great majority of cases.[9,10] This may have been due to the fact that *complete* ligation has been employed by most observers. In the experiments reported here the wall of the dilated ureter was found to be much hypertrophied in the majority of instances and microscopic

* For the most satisfactory composition of Locke's solution, see note 7.

† It was found necessary to use the finest needles and silk such as are employed in suturing bloodvessels. The needles were blunted a little to ensure against injury to the wall of the ureter after passing through it.

examination showed that this occurred in all three muscle layers. In three experiments the rubber bands cut quite through the wall of the ureter. In two of these cases the ureter had reëstablished its lumen and apparently functioned as before ligation. Two of the

FIG. 1.—Dog 128, June 25. Normal ureter in Locke's solution. The peristaltic waves were complete. The bladder end of the ureter acted as pacemaker throughout the experiment; time marked in five-second intervals.

rubber bands were found free inside the hydronephrotic sac. Caulk and Fisher[10] have shown that the lumen may be restored after complete ligation by epithelial outgrowths of the wall from above and below the ligation in six weeks' time.

FIG. 2.—Normal ureter excised from a dog that had had no previous operation. The ring segments contracted independently throughout the experiment. This form of curve with groups of rapid contraction separated by long intervals of rest was exhibited by the bladder end of the ureter in several experiments.

In each case where there had been no interference with the ureter the direction of peristalsis was from renal pelvis to bladder, even when the ureter was dilated to over 1 cm. in diameter. In such cases the pressure throughout must have been the same. This would show that the stimulus of the pressure of freshly secreted

urine in the pelvis is not necessary to inaugurate peristaltic waves at this point.

When the ureters were excised and suspended in oxygenated Locke's solution as described above the origin of spontaneous peristaltic waves varied. This was true of both the normal and dilated ureters. Waves were as likely to pass up as down the ureter or even to alternate. In six cases it happened that few or no complete peristaltic waves occurred. Instead the segments at the two ends contracted independently. In three of these latter experiments the rate of contraction of the segment at the pelvic end was faster than that at the other end. In the other three experiments the rates at the two ends were about the same. No consistent difference in the conformation of the curve made by the contraction of rings at different levels was noted, as mentioned by Satani when working with pigs' ureters.

Observations were made on the action of a few of the more important drugs on the excised ureter, but no exhaustive study of the pharmacology of the ureter was undertaken.*

It has been observed by numerous experimenters that antiperistalsis may be induced by mechanical stimulus applied directly to the ureter. Levin and Goldschmidt[14] in 1893 caused a passage of colored solution from the bladder to the pelvis of the kidney by mechanical stimulation of the bladder. No reference to a repetition of these experiments was found in the literature of the ureter. In 1911 Cannon[15] showed the possibility of inducing antiperistalsis in the colon. He observed the formation of a local constriction ring following stimulation mechanically or with barium chloride, and that this ring beat rhythmically, thus inaugurating simultaneous waves of peristalsis and antiperistalsis. Up to this time nothing analogous to this has been demonstrated in the ureter.

In experiment 10 the abdomen was opened, the intestines reflected upward and the rabbit placed in a warm box as usual. The dilated ureter was pinched between forceps. A ring of con-

* In view of the recent stimulating work on the pharmacology of the ureter by Macht,[11 12 13] and still more recently by Satani,[8] it may be of interest to note the effect of a few drugs on the whole excised ureter of a dog, as distinguished from the separate ring segments of pig ureters used by the two above-mentioned experimenters. In both normal and hypertrophied ureters epinephrin produced an increased rate of contraction. No effect on the conductivity was detected and the two ends responded equally. 0.015 gm. papaverin in 50 c.c. Locke's solution decreased the tone of the ureter and the rate and amplitude of contraction. The bladder end, in fact, was quickly paralyzed while the pelvic end continued at a slower rate. Nicotin caused a marked increase in the tonus and rate of contraction at both ends, which was followed by paralysis. Pilocarpin and atropin were added to Locke's solution in four cases. In three there was no effect. In the fourth, after the addition of 0.13 gm. pilocarpin to 50 c.c. Locke's solution, there was a small but definite increase in the rate of both the pelvic and bladder segments. This was followed by 0.013 gm. atropin, which made the contraction rate a little slower. In these experiments these two last drugs had very slight effect on the ureter, if any, and one would be led to suppose that in therapeutic doses they would have no effect.

traction formed at once and in a few seconds a single contraction wave was sent out simultaneously in each direction. After this, however, the area acted as a block, arresting the spontanous waves of peristalsis from above and thus permitting the lower half of the ureter to contract independently. At a rate much slower than the previous normal peristalsis, waves of retroperistalsis passed from a point in the ureter just above the bladder upward to the block. This continued for about fifteen minutes. During this time the traumatised area acted like a Stannius ligature on the heart, cutting off stimuli from the normal pacemaker in the pelvis or pelvi-ureteral junction.

In experiment 14, performed on a rabbit, it was found that the application of a drop of dilute solution of barium chloride to the dilated ureter *in situ*, resulted in the production of a local ring of tonic constriction. From this point, at intervals of about twenty seconds, waves of contraction were sent off simultaneously in both directions. This area of increased tonus could not be seen to beat, as could the rings in the colon described by Cannon, but otherwise the phenomena are quite similar. It is probable that if the ureter were larger the ring would be seen to beat with the inauguration of each contraction wave. Later, normal waves of peristalsis originating at the pelvis recurred and the antiperistalsis ceased. Moderate pressure upon this hydro-ureter showed that urine could be forced out through the constricting rubber band. In experiment 27, this time on a dog, the occlusion of the lumen of the dilated ureter was functionally complete, as no urine was seen to emerge from the ureteric orifice into the bladder following peristaltic waves. On this ureter the above experiment was repeated with a similar result, waves passing outward in both directions from the ring of increased tonus every four seconds.

Discussion. In the last two experiments above cited the constriction ring became pacemaker and controlled the whole ureter, in virtue of the fact that its rhythm was more rapid than the rhythm of spontaneous contraction in any other part of the ureter or pelvis. The rate of discharge from the rings in the two cases was twenty and four seconds respectively. When the irritability of these areas had become less the rhythm became slower and the pelvis returned to its role of inaugurating peristalsis.

In those cases in which the proximal and distal rings beat independently in Locke's solution the rate of the kidney ring was more rapid than that of the bladder ring in a rather small majority of cases. But in those cases in which spontaneous peristalsis was complete *in vitro* the location of the pacemaker was found to be in one end as frequently as in the other. Satani found that the single excised segments of ureter from the pelvic end beat more rapidly in Locke's solution than segments from the other end. Boulet and Gley[16] observed that the upper segment of a human

ureter contracted more rapidly in Locke's solution than the lower segment. Stern[17] observed normal ureteral peristalsis two weeks after nephrectomy. We may conclude that the rhythmicity of the upper ureter is usually more rapid than that of the lower end, but the fall in rate is not very marked and the difference easily upset. There is an area in the pelvis, however, whose rate of spontaneous contraction is much above that of the ureter. Nagel[18] noted that after making a section at the pelvi-ureteral junction the pelvis continued to contract without interruption. In some of the present experiments, in which the ureter was distended to the most extreme degree, it was noted on opening the abdomen that the contraction caused by the peristaltic wave at the upper end of the ureter was so weak as to be scarcely visible, but a shadow-like wave always began at the pelvis and passed downward to the lower ureter where the distention was usually less and the contractions always more vigorous. There is, therefore, an area in the renal pelvis whose spontaneous contraction rate is normally higher than that of any part of the ureter and which acts as pacemaker.

Child[19] has shown that tissues with a rapid rate of oxidation are more susceptible to certain poisons, *e. g.*, KCN, than tissues with a slow rate. He showed in ctenophore that in passing from the aboral to the oral end there is a gradation of susceptibility to the poison and a corresponding gradation in the metabolic activity at the successive levels. He proposed the hypothesis that all axiate organisms, as well as all axiate structures in complex organisms, have a gradient of metabolism underlying their activity. As examples of axiate structures or organs, take the intestine, the Fallopian tubes or the ureter. According to Child, that area will dominate the whole organ which has the highest rate of metabolism. Peristaltic waves will follow a definite gradient of forces passing from an area of high rate of metabolic activity to areas of lower rate. This descending pathway is called the metabolic gradient. Hyman[20] showed that regions of high metabolic rate are electropositive, internally, to regions of lower metabolic rate. Tashiro[21] demonstrated a metabolic gradient as measured by CO_2 production in nerves. This gradient he found to be in the direction followed by nervous impulses within the cells and their processes. Alvarez[22] found that the spontaneous contraction rate of excised segments of intestine beating in Locke's solution falls progressively in passing from duodenum to terminal ileum. He later observed that this gradation of rhythm corresponds to a like gradation in CO_2 production of segments at rest and contracting,[23] and with the production of catalase[24] in the whole gastro-intestinal canal. He concludes that the direction of peristaltic waves in the gastro-intestinal tract follows underlying gradients of metabolism and that disturbances in peristalsis are related to alterations of local metabolic rate induced by trauma, poisons, inflammation, etc.

If the generalizations of Child be taken as a working hypothesis it must be assumed that there is normally an area in the renal pelvis whose metabolic rate is higher than that in any part of the ureter and that also there is usually a downward metabolic gradient from the pelvic to the bladder end of the ureter. But the difference between the metabolic rates at the two ends of the ureter must be so small as to be easily upset by abnormal conditions. It is not necessary to infer that, after its inauguration, the path of the peristaltic wave is constantly along a downward metabolic gradient. For example, in experiment 10, as noted above, the pacemaker for the whole ureter was in the renal pelvis; but after injury to the ureter at its middle, sufficient temporarily to cut off the lower half from stimulation from above, it became apparent that in this isolated segment the rate of metabolism was greatest at the distal end, thus causing retroperistalsis.

At the time of the first operation the accompanying vessels were carefully reflected before ligation of the ureter, so that the extrinsic blood and nerve supply should not be disturbed. Intrinsic blood supply and intrinsic nerves were doubtless functionally severed. Aside from this the dilated ureter differed from the normal ureter only in its reaction to distention, *i. e.*, (*a*) muscular hypertrophy, in most cases, (*b*) increased rate of peristalsis. (These peristaltic waves were sometimes incomplete.)

The conditions in the colon described by Cannon[15] in 1911 are reproduced in the hydro-ureter. His explanation of the rhythmical contraction inaugurated by the constriction ring in the gut was briefly as follows: There are three principal underlying factors: (*a*) A ring where the smooth muscle fibers were shortened and tonus increased, (*b*) distention, (*c*) refractoriness. Smooth muscle when in a short state is extended more readily by a moderate load than by the same load when it is in a long state.[25] The ring is stimulated to contract by distention, for withdrawal of the colonic contents stopped the pulsations while return of the contents restored them. Refractoriness to stimulation during contraction and the early part of relaxation was held to explain the rhythmicity.

The hydro-ureter is likewise a distended tube of smooth muscle which, like the colon, has an intrinsic innervation. This innervation of the ureter, however, is derived from the sympathetic system while that of the colon comes from the bulbosacral outflow.[26] Increased tonus and more rapid rhythmicity followed the local application of barium chloride to the ureter. What was the process?

Tashiro[21] found that stimulation of plant or animal tissue always caused increased CO_2 production. Barium chloride is a stimulant of smooth muscle. The process of oxidation is therefore made more rapid in the area of application. In other words, in the constriction ring, metabolic activity is increased and there must be a downward gradient of metabolism from the ring to all other parts of the ureter.

It may be urged that increased CO_2 production and other evidences of cell activity are due only to a greater amount of work done in areas inaugurating peristaltic waves. But the cardia of the stomach does less work than the pyloric end, and yet Alvarez[23] found that, associated with its function of pacemaker and more rapid spontaneous contraction when excised, there was greater production of CO_2 and of catalase in the cardia.

Increased tonus exists at the constriction ring in the ureter as in the colon, but more fundamental than this is an increase in the rate of tissue metabolism. Therefore the rhythm of the constriction ring may be attributed to (*a*) a higher rate of metabolism, (*b*) distention, (*c*) refractoriness.

The ureter deserves more careful investigation along these lines and a better understanding of the physiology of the normal and dilated ureter is of the utmost importance in clinical urology. It has been noted above that slight local trauma to the ureter causes a wave of contraction to be sent out in each direction from the injured area. Hyman[20] showed that *injured areas* have an increased metabolic rate and Segale[27] that *inflammation* is associated with increased biochemical cellular activity. It may be suggested that in the passage of a renal calculus it is quite possible that the injury inflicted by a sharp stone upon the ureteral walls may cause the inauguration, at this point, of waves of peristalsis and retroperistalsis. In addition to these isolated contraction waves, which are undoubtedly sent out thus from time to time, conditions are evidently reproduced clinically which in the above experiments caused the formation of a constriction ring. For in addition to increased local metabolism there must be a certain amount of distention following the action of the stone as a partial plug, especially after local contraction of the ureter about it. The kidney would continue to secrete urine until the intrapelvic pressure reached a point 40 to 50 mm. Hg below the blood-pressure.[28]

Trauma and inflammation about the stone are sufficient to cause a local increase in metabolic rate. With the appearance of distention all the conditions necessary for the creation of a constriction ring would be fulfilled. Lucas[5] demonstrated that, normally, the action of the ureter will provide for a neutral or negative pressure of urine in the kidney pelvis even against a resistance of 15 cm. of water pressure. He reported that he had seen the middle portion of the excised ureter of a small dog raise a column of water 72 cm. If, then, retroperistalsis were produced by a constriction ring as suggested above a considerable degree of pressure could be induced in the pelvis.

This would seem a more plausible cause of renal colic than local irritation or supposed ureteral efforts to dislodge the stone or only the passive dilatation of the pelvis by the secretion of urine against

back pressure from a plugged ureter. Osler,[29] describing renal colic from personal experience, speaks of "flushes or rushes of hot pain at intervals, often momentary, usually passing to the back, less often toward the groin." Also during pyelography, when the radiographic fluid is introduced into the pelvis under pressure through a ureteral catheter, patients frequently complain that the pain induced is similar to renal colic.

The suggested sequence of factors causing renal colic is, then, (*a*) trauma and probable inflammation of the ureter wall about the calculus, (*b*) contraction down upon the calculus causing temporary occlusion of the ureteral lumen, (*c*) increased pressure in the pelvis and ureter followed by moderate distention, (*d*) rhythmical contraction waves passing out simultaneously in both directions from the stone.

Definite proof that retroperistalsis occurs in renal colic cannot be offered, but the experiments reported above and the demonstration of constriction rings in the ureter make such a hypothesis worthy of careful consideration.

SUMMARY. Unilateral, incomplete ligations of the ureter were performed in a series of thirty-two rabbits and dogs. At a subsequent operation the ureters of the rabbits were observed *in vivo*. In the case of the dogs, after observation *in vivo*, both ureters were removed and placed in Locke's solution, where a ring preparation was made at either end of the intact ureter and contraction curves graphically recorded.

Extreme dilatation, more marked proximally, and in most cases hypertrophy of the muscle walls, resulted. In two cases the rubber band ligature cut through and the lumen of the ureter was restored.

In oxygenated Locke's solution it was possible to record the beginning and end of peristaltic waves which passed throughout the length of the ureter. These complete spontaneous waves originated at either end with equal frequency. In cases in which the segments of the two ends contracted independently the rate of the pelvic ring was, on an average, a little more rapid than that of the bladder end. There was no consistent difference noted in the size and form of the contraction curves at the two ends in either the normal or hydronephrotic ureter. The effects of certain drugs were noted.

Peristalsis in the unmolested ureter always began in the pelvis even in cases of extreme dilatation, in which fresh secretion of urine into the pelvis could not be a factor in causing the inauguration of the waves at this point. Mechanical or electrical stimulation of the ureter at any point caused a wave of contraction to pass outward in each direction. In one experiment trauma to the midpoint of the ureter produced a refractory area here which blocked waves from above. There then appeared waves of antiperistalsis arising near the bladder and passing upward to this block.

A crystal or drop of barium chloride applied to the hydronephrotic ureter *in vivo* caused a narrow ring of tonic constriction. From this, at a rapid rate, simultaneous waves of peristalsis and antiperistalsis passed out in both directions to the extremities of the ureter. This constriction ring is analogous to that described in the colon by Cannon.

CONCLUSIONS. The ureter is a muscular tube which, when subjected to partial obstruction, always dilates, usually hypertrophies, and whose peristaltic rate is increased.

Contraction waves pass in either direction with equal facility, depending on the location of the area whose rate of spontaneous contraction is most rapid. This area is normally in the renal pelvis, but under abnormal conditions a more rapid pacemaker may be established elsewhere. From the analogy to other axiate organs, it is suggested that underlying the more rapid rhythm of the pacemaking area is the fact that its metabolic rate is more rapid than that in any other level of the ureter.

Production of a constriction ring which becomes pacemaker for the ureter above and below it depends on three things: the metabolic gradient, ureteral distention and refractoriness during contraction and the first part of relaxation.

It is suggested that in the passage of a ureteral stone, trauma and inflammation increase the rate of metabolism in the ureter wall about the stone, a constriction ring results, followed by distention of the ureter and retroperistalsis. This would cause great distention of the renal pelvis and give to renal colic its peculiar rhythmical character.

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DIETS FOR THE AMBULANT TREATMENT OF DIABETES MELLITUS.

By Herman O. Mosenthal, M.D.,

and

Herbert J. Wiener, M.D.

New York.

(From the Department of Metabolism, Vanderbilt Clinic, New York City.)

The modern treatment of diabetes mellitus in hospitals and sanatoria is a highly organized procedure. It demands the expert work of dietitians, laboratory technicians and especially trained nurses, in addition to medical supervision, and it requires the aid of a properly equipped laboratory and diet kitchen. By these means the diabetic, on leaving the hospital, has been taught, as a rule, how to examine his urine for sugar and diacetic acid, and has had some instruction in the principles underlying his diet. But for the uneducated patient, even after such a training, it is exceedingly difficult to devise menus with specified amounts of protein, fat and carbohydrate according to his needs, nor can the workingman or woman easily spare the time required for this important task. The rich, as a rule, solve the problem by putting a specially trained nurse in charge, but for the poor it is often impossible to meet the requirements of the situation.

The following lists have been prepared in order to bring weighed

diets to their simplest possible terms. They have been designed especially for diabetic patients who are able to be up and about attending to their routine duties, and not endowed with unlimited means. The successful management of such patients depends largely upon the ease with which they are enabled to follow the prescribed dietary regime. By the use of these diet lists the physician can readily control the total caloric intake as well as the relative amounts of protein, fat and carbohydrate consumed, while at the same time the essential coöperation of the patient is reduced to a minimum in time and mental effort.

The measured diets in the modern treatment of diabetes must meet two requirements: (1) Control of the glycosuria, and (2) control of the acidosis. The first of these is accomplished by regulating the consumption of the carbohydrates and the second by adjusting the fat intake. The greatest recent advance in the management of diabetes mellitus is the recognition of the fact that a curtailment of the fatty foods will prevent or postpone acidosis and coma. Two sets of diets are necessary, therefore: (1) In which the fats are reducted to a minimum, and (2) in which fats are allowed more liberally, but in limited amounts. The latter is the preferable diet to use when possible, as it is much the more palatable when continued for a long time. Accordingly, two diets have been designed, one the so-called "minimal fat diet" (Tables I, II and III) and the other the "low fat diet" (Tables III, IV and V); in both of them the only carbohydrate is that contained in the green vegetables.

TABLE I.—MINIMAL FAT, STARCH-FREE DIET.

Calories	500	750	1000	1250	1500
BREAKFAST:					
Black coffee or plain tea (no sugar) as desired.					
Meat or fish (see Table II for kind and amount) portion	A	B	C	C	E
Vegetables from list, heaping tablespoonful, ready to serve	4	4	4	4	4
DINNER:					
Clear meat broth, plain, as desired					
Meat or fish, from list, portion	B	C	D	E	F
Vegetables from list, ready to serve, heaping tablespoonful	4	4	5	6	6
Pot cheese, heaping tablespoonful	none	none	none	1	1
Gelatin jelly, flavored with coffee and saccharin, heaping tablespoonful	none	none	2	2	3
Black coffee or plain tea (no sugar) as desired.					
SUPPER:					
Clear meat broth, plain, as desired					
Meat or fish, from list, portion	B	C	D	E	E
Vegetables from list, ready to serve, heaping tablespoonful	4	4	5	5	6
Black coffee or plain tea (no sugar) as desired.					
SPECIAL ORDERS:					
Saccharin, if desired, five tablets or less during whole day.					
No butter, fat or oil to be used in cooking.					

TABLE II.—MEAT AND FISH PORTIONS FOR USE WITH THE MINIMAL FAT, STARCH-FREE DIET.

	Ounces of food weighed raw.					
MEATS: Portion.	A	B	C	D	E	F
Beef—Soup meat, fore-shank, lean	3	4½	7¼	9	11¾	14¾
Dried beef	1½	2½	4½	5	6¾	8¼
Lean round steak	2¼	3½	5¾	7	9½	11½
Lean roast beef (no visible fat)	2¼	3½	6	7	9½	11¾
Kidney	3	4½	7½	9	12	15
Chicken	3	4½	7½	9	12	15
Lean leg of lamb (no visible fat)	1¾	2½	4	5	6¾	8¼
Tripe	5¾	8¼	14	16¾	22	27¾
Lean veal (no visible fat)	2¾	4	7	8	11	13½
FISH (Fresh only):						
Bluefish	4	6	10	11¾	15½	19½
Codfish	4½	6½	11	13	17½	22
Flounder	5½	8¼	14	16½	22	27½
Haddock	4¾	7	11¾	14¼	19	23¾
Sea bass	4¼	6¼	10½	12½	16½	21
Sheepshead	3	4½	7½	9	12	15
Smelts	4	6	10	11¾	15½	19½
Weakfish	3¾	5½	9¼	11	14¾	18½

TABLE III.—LIST OF VEGETABLES TO BE USED IN BOTH THE MINIMAL FAT AND LOW FAT DIETS.

Asparagus	Onions, cooked
Asparagus tips	Pickles, sour or dill
Brussels sprouts	Pumpkin
Cabbage	Radishes
Cauliflower	Rhubarb
Celery	Sauerkraut
Cucumbers	Sorrel
Egg plant	Spinach
Endive	Stringbeans
Greens from beets	Swiss chard
Kohlrabi	Tomatoes
Leeks	Watercress
Lettuce	Wax beans

The minimal fat diet is graded by 250 calory steps from 500 to 1500 calories. It is not feasible to increase the diet beyond this point, because when proteins make up the greater part of the nourishment, as they necessarily do in the minimal fat diet, the bulk of food becomes too great. It is even problematical whether all patients can consume the amounts designated under the 1250 and 1500 calory diets. However, the safest way to curtail the food in diabetics suffering with severe acidosis or threatened coma is first to restrict the fats. By means of the present list (I, II and III), this can easily be done. Carbohydrates may be added if it is thought advisable.

TABLE IV.—LOW FAT, STARCH-FREE DIET.

	Calories.	500	750	1000	1250	1500	1750	2000
BREAKFAST:								
Black coffee or plain tea (no sugar) as desired								
Eggs		1	1	1	2	2	2	2
Meat or fish (see Table V for kind and amount) portion		A	B	B	C	D	E	F
Butter, flat teaspoonful		none	1	1	2	2	3	3
DINNER:								
Clear meat broth, plain, as desired								
Meat or fish, from list, portion		B	D	E	E	F	F	F
Vegetables, from list, ready to serve, heaping tablespoonsful		4	4	5	6	6	6	6
Pot cheese, heaping tablespoonful		none	none	none	none	none	1	1
Olive oil, teaspoonsful		none	none	2	2	2	3	3
Butter, flat teaspoonsful		1	1	2	2	2	3	4
Black coffee or plain tea (no sugar) as desired								
SUPPER:								
Clear meat broth, plain, as desired								
Eggs		none	none	none	none	1	1	2
Meat or fish, from list, portion		B	D	E	E	F	F	F
Vegetables from list, ready to serve, heaping tablespoonsful		4	4	5	5	6	6	6
Butter, flat teaspoonsful		1	1	1	2	2	3	4
Black coffee or plain tea (no sugar) as desired								
SPECIAL ORDERS:								
Saccharin, if desired, five tablets or less in a day.								
No extra butter, oil or fat to be used in cooking.								

For practical purposes of rough measurement the table and teaspoonful portions are adequate and exact within a reasonable margin of error. The portions of meat and fish are calculated to within the nearest ¼-ounce value. One-quarter ounce is probably closer than the average scales of the butcher or home can weigh accurately, but in giving the amounts in these fractions an indication is furnished on what side allowances should be made. The actual use of these diet lists is self-explanatory.

A concrete idea of the proportion of proteins and fats in these diets may be gained from Tables VI and VII. In the minimal fat diet the ratio of protein to fat is found to be about 3 to 1 when round steak is eaten as the meat or fish, and 17 to 1 when blue fish is used (Table VI). This, in either case, furnishes a very low fat intake. When the lowest possible quantity of fat is required it is evident that fish is more desirable than meat.

TABLE V.—MEAT AND FISH PORTIONS FOR USE WITH THE LOW FAT, STARCH-FREE DIET.

		Ounces of food weighed raw.					
MEATS:	Portion.	A	B	C	D	E	F
Bacon, fried, fat thrown away	1	1½	1½	2½	3	3½	5
Brain	1	2½	3	3½	6	7½	9½
Chicken (to be boiled or broiled)	1	2½	3	5½	6	7½	10
Chicken (to be roasted)	1	1½	1½	2½	2½	3½	4½
Corned beef	1	1	1½	2½	2½	2½	3½
Dried beef	1	1½	1½	3	3½	4½	5½
Duck	1	1¼	1¼	2½	2½	3½	4½
Ham, smoked (to be boiled or broiled)	1	1	1½	2½	2½	3	4
Guinea hen	1	2	2½	4½	4½	5½	7½
Kidney	1	2½	3	5½	6	7½	10
Lamb chops	1	0	1	1½	2	2½	3½
Lamb (to be roasted)	1	1	1½	2½	2½	3	4
Mutton (to be boiled)	1	1½	2	4	4½	5½	7
Mutton chops, lean	1	2½	2½	4½	5½	6½	8½
Mutton (to be roasted)	1	1	1	2	2½	2½	3½
Pork (to be roasted)	1	1½	1½	3	3½	4½	5½
Pork chop, lean (to be broiled)	1	2	2½	4	4½	5½	7
Roast beef	1	0	1	1¼	2	2½	3½
Soup meat, fore-shank, lean (to be boiled)	1	2½	3	3½	6	7½	9½
Squab	1	1½	1½	3	3½	4½	5½
Steak, round, lean	1	2	2½	4½	4½	5½	7½
Steak, sirloin, lean	1	1½	2	3½	4	5	6½
Tongue, fresh (to be boiled)	1	1½	2½	4	4½	5½	7
Tongue, boiled, smoked, cold	1	1	1	2	2½	2½	3½
Veal, roast or chop, lean	1	2½	2½	4½	5½	6½	8½
	Portion.	A	B	C	D	E	F
FISH (Fresh, to be boiled or broiled):							
Bass, black	1	3	3½	6½	7	9	11½
Bass, sea	1	3½	4½	7½	8½	10½	13½
Bluefish	1	3½	4	7½	7½	9½	12½
Butterfish	1	1½	2	3½	4	5	6½
Codfish	1	3½	4½	8	8½	11	14
Flounder	1	4½	5½	10½	11	14	18
Haddock	1	4	4½	8½	9½	12	15½
Halibut	1	2½	2½	5½	5½	7½	9½
Kingfish	1	3½	4	7½	8	10	13
Mackerel	1	2	2½	4½	5	6½	8
Perch	1	3½	4½	7½	8½	10½	13½
Pike	1	3½	4½	8	8½	11	14
Porgy	1	2½	2½	5½	5½	7½	9½
Salmon	1	1½	1½	3	3½	4½	5½
Sheepshead	1	2½	3	5½	6	7½	9½
Smelts	1	3½	4	7½	8	10	13
Weakfish	1	3	3½	6½	7½	9½	12
Whitefish	1	4	4½	8½	9½	12	15½
CANNED OR SMOKED:							
Herring, smoked	1	1	1½	2½	2½	3	3½
Salmon, canned	1	1½	1½	3½	3½	4½	5½
Sardines in oil	1	1	1½	2½	2½	3	4
Sturgeon, smoked	1	1¼	1½	3	3½	4	5½
Tunnyfish in oil, canned	1	1	1½	2½	2½	3	4

TABLE VI.—APPROXIMATE QUANTITIES OF PROTEIN, FAT AND CARBOHYDRATE IN THE MINIMAL FAT, STARCH-FREE DIET WHEN ROUND STEAK OR BLUEFISH ARE USED AS MEAT OR FISH.

Minimal fat diet when round steak is used as meat or fish.	Protein, gm.	Fat, gm.	Carbohydrate, gm.
500 calories	60	20	18
750 "	93	33	18
1000 "	126	43	21
1250 "	159	54	24
1500 "	194	66	25
When blue fish is used as meat or fish.			
500 calories	88	4	18
750 "	148	8	18
1000 "	193	12	21
1250 "	244	14	24
1500 "	298	18	25

Table VII gives the relative values of protein, fat and carbohydrate when roast beef, round steak or flounder are used as the meat or fish in the low fat diet. These particular foods were selected because they represent a high, average and low fat content for these diets. When roast beef is eaten the fat is higher than the protein; with the flounder the ratio is reversed. The low fat diet, when the patient chooses his own food, has been calculated and found to contain, as a rule, proteins and fats approximately equal gram for gram.

TABLE VII.—APPROXIMATE QUANTITIES OF PROTEIN, FAT AND CARBOHYDRATE IN THE LOW FAT, STARCH-FREE DIET WHEN ROAST BEEF, STEAK OR FLOUNDER ARE USED AS MEAT OR FISH.

Low fat diet when roast beef is used as meat or fish.	Protein, gm.	Fat, gm.	Carbohydrate, gm.
500 calories	22	39	12
750 "	33	71	12
1000 "	39	83	15
1250 "	50	106	17
1500 "	66	126	18
1750 "	75	149	19
2000 "	85	169	19
When steak is used as meat or fish.			
500 calories	44	29	12
750 "	72	44	12
1000 "	87	64	15
1250 "	105	83	17
1500 "	134	97	18
1750 "	147	118	19
2000 "	164	136	19
When flounder is used as meat or fish.			
500 calories	73	16	12
750 "	122	22	12
1000 "	149	37	15
1250 "	172	52	17
1500 "	217	59	18
1750 "	235	77	19
2000 "	259	92	19

In the low fat diets there is no difficulty, as far as bulk of food is concerned, in consuming as much as 2000 calories. As Mosenthal and Clausen[1] have shown a carbohydrate-free diet of 1500 to 2000 calories, containing approximately the same proportion of protein and fat as the present list, will maintain the nitrogen equilibrium of the diabetic and may be considered to furnish the patient with enough food to make him mentally and physically efficient. If the carbohydrate tolerance of the patient permits of a still further increase in the food it is best to add starch-containing foods and not proteins or fats.

The above food lists are presented in the belief that they will furnish a practical means of regulating the diet of sufferers from diabetes mellitus who are not receiving hospital treatment, and who, while under medical supervision, are dependent upon their own resources for the details of dietetic control. These diets are not intended in any way to supplant the more accurate and ideal means of weighing and measuring food if these are available.

ACUTE INFECTIOUS ENTERITIS WITH A POLYNEURITIC SYNDROME.

By Frederic J. Farnell, M.D.,

VISITING NEUROPSYCHIATRIST, PROVIDENCE CITY HOSPITAL; CONSULTANT IN NEUROPSYCHIATRY TO RHODE ISLAND STATE HOSPITAL FOR MENTAL DISEASES AND ST. JOSEPH'S HOSPITAL,

AND

Arthur H. Harrington, M.D.,

MEDICAL SUPERINTENDENT, RHODE ISLAND STATE HOSPITAL FOR MENTAL DISEASES, HOWARD, RHODE ISLAND.

The action of bacterial poisons upon the peripheral and central nervous system is a source of great interest to the neuropathologist whether he be applying principles or producing lesions experimentally. One has only to recall that most serious epidemic of poliomyelitis in New York in the year 1916 to recognize the vast importance of how rapidly an infection may attack the central nervous system, and yet sufficient data is lacking in regard to the exact etiology and the mechanism of the action of the virus still remains unexplained.

The obscurity which surrounds the cause of many of the inflammatory processes which attack the various systems, gastro-intestinal, nervous, etc., as is seen in practice in institutions, is a fact which one must admit. There is hardly an institution throughout the

[1] Arch. Int. Med., 1918, xxi, 269.

country which, at some time or other, does not have an epidemic of "asylum dysentery," "amebic dysentery," "pellagra" or what not. But the epidemic here under discussion, as observed by Dr. Harrington and myself in the summer of 1917, at the State Hospital for Mental Diseases, at Howard, Rhode Island, warrants comment, not only from the standpoint of the clinical picture, as one of an infectious enteritis with a polyneuritic syndrome, but also from the standpoint of its mechanism, as pointed out by its pathology, both clinical and tissue. A statement will also be made as to the possible selective action of certain bacteria, especially so in variable phases of their evolution.

Orr and Rows have offered much valuable data as to the lymphogenous infection of the central nervous system, and Rosenau has emphasized the possibility of the selective action of bacteria which bears, probably, a close relation to the various stages in its evolution. Much experimental work has been performed in an attempt to demonstrate the relation of the lymph stream to the peripheral nerves and to the spinal cord itself. In 1902 Homan and Laitnen injected streptococci into the sciatic nerves of animals, and was able to trace the bacteria into the meninges of the cord. Pirrone, in 1905, used as his infective agent the pneumococci and found changes in the cord limited to the side corresponding to the infected nerve. These investigators, therefore, concluded there must be a common lymph system for the posterior roots, the posterior columns and pia covering them, and that the lymph flows freely in the various channels between the fibers and other structures. It is upon this basis that syphilographers have based their conclusions in relation to the origin of tabes: that is, the syphilitic infection or toxin makes its entrance into the lymph stream and passes along the nerve trunks to the posterior roots and thence to the posterior columns. However, actual data as to this mechanism has not been thus far demonstrated, and is held only on theoretical grounds.

Homan's investigations, however, are still convincing in this point. Twenty-four hours after the injection of the bacteria into the sciatic nerve (streptococci) it is found that they accumulate in the lymphatic space situated on the internal surface of the perineurium, and that this can be traced along to the internal surface of the capsule and the spinal ganglia, then along the inner surface to the spinal roots and into the meninges, from which they spread into the peripheral zone of the cord, and especially so along the posterior median septum. Throughout this entire invasion there is an accompanying inflammatory reaction which, pathologically, might be considered an ascending inflammatory perineuritis. These experiments and conclusions call into play many theories regarding such processes as herpes zoster, anterior poliomyelitis, which is an acute inflammation of the anterior horn cells, and beriberi, which is a polyneuromyositis of the toxic type. Of course, it must be duly considered

that in experimental work, in order to bring about distinct changes in the tissues, there is undoubtedly a possibility of the diffusion of inflammatory processes along the nerves to the central nervous system; but even admitting such a condition as a diffusion, it is of rather minor importance as compared with the fact that these organisms and toxins do reach the central nervous system, and that they probably make their way there through the lymph channels.

It is a rather interesting coincidence, in reviewing the literature, to find that Orr and Ross, in performing their experiments, used as their bacterium the staphylococcus. The series of cases that followed at the State Hospital, in the recent epidemic, also in a large percentage of cases examined, showed the presence of staphylococcus. Orr was able to cultivate, after repeated injections, a strain of staphylococcus whose virulence was very marked and whose activity upon the tissues was extreme. It is a well-recognized fact that the Staphylococcus aureus varies greatly in its virulence and that the virulence of even one strain may be enhanced or decreased in its passage through the individual's body. A prolonged cultivation will decrease its virulence. Here, again, experimentally, various forms of visceral lesions have been produced by inoculation. Rosenau has produced endocarditis, myositis, neuritis and other acute inflammatory processes in various parts of the human body by the inoculation with strains of streptococcus as well as staphylococcus of a prolonged cultivation, and he is of the opinion there are stages in the evolution of all bacteria which will produce a body reaction for that particular stage in which it happens to enter the body.

In experimentation, either by the lymphogenous or the hematogenous paths, one of two types of inflammatory processes may occur: one an acute inflammatory reaction with secondary degeneration, probably due to the extreme diffusion of the lesion, and the other an acute degenerative process, primary type.

The writers present this paper as the clinical and pathological report of a series of cases of infectious origin which occurred during the interval from July 15 to August 6, 1917. The highly infectious or communicable nature of the disease process was not apparent at its start, because the clinical symptoms lacked uniformity. The daily increasing number of cases, however, with the acute gastrointestinal symptoms and the accompanying involvement of the nervous system in a number of instances, made it obvious that one was dealing with a serious condition, and one, probably of an infectious type. As soon as this became apparent, arrangements were made to isolate and quarantine in two wards, which were prepared for this purpose, all cases believed to be suffering from this disease.

A systematic investigation was begun immediately in an endeavor to discover any cases which might exist throughout the wards of the hospital. This may account in some degree for the recognition

of additional cases during the last week of July and the first week of August, but the acuteness of the symptoms and the complaints of more receptive patients, who became affected, aided us materially in discovering instances of the trouble.

Forty-seven patients and four employees were quarantined. There were twenty other individuals whose symptoms were so mild that they were regarded only as suspicious cases; it is possible that they may have been mild or abortive instances of the disease. These later cases made a prompt recovery.

A watch was kept for the outcropping of cases on the male side of the hospital, but none came to light. Therefore, all the cases of the disease herewith described were in women patients.

The general onset of the clinical symptoms were acute gastro-intestinal disturbances, characterized by nausea and vomiting, frequent discharges from the bowels, containing mucus, or in some both mucus and blood; there was a rise in temperature to 100° and as high as 104°. In a large number of the cases there was great prostration, with headache and backache. The neuritic symptoms presented what appeared to be a peripheral neuritis, involving either the lower extremities or merely the upper extremities, and yet in a number of cases both the upper and lower extremities seemed to be involved. In these regions there was excessive pain on slight pressure in some of the cases, while in others there was pain over the muscles and nerve trunk only on deep pressure. In several cases the fear of being touched would cause the patient to cry out and the slightest brushing of the bed-clothes or touch of a camel's-hair brush caused excessive pain. The reflexes, especially the patella, were absent on both sides as a general rule, but in a few cases only on one side. The Achilles reflex was absent on one or both sides. With regard to walking and the coördinative mechanism there was great weakness. Some could stand only with help, but could not walk. In those whose upper extremities were affected there was a clumsiness in the use of the arms and hands. In a few cases there was a complete paralysis of the lower motor neuron of both the upper and lower extremities.

The early cases were the most severe and showed the slowest improvement. They were more uniform in their clinical manifestations after the disease process was once recognized than the later ones were. The early cases showed, to a marked degree, the neuritic symptoms as well as the gastro-intestinal. In the later cases the main force of the disease seemed to be exerted either on the gastro-intestinal tract or on the nervous system.

It seemed feasible to divide the cases which were isolated and quarantined into three groups, clinically considered. In the first group would fall 19 cases in which the gastro-intestinal symptoms were well marked, even severe in some instances, and in which the neuritic syndrome was also especially prominent. In the second

group were 7 cases in which the gastro-intestinal symptoms were serious and in 1 fatal, but in which the neuritic symptoms, while unmistakably present, were less so in degree than in the first group. In the third group were 21 cases in which the gastro-intestinal disturbance was the feature of the disease and only a few disclosing little or no evidence of a peripheral neuritis. Brief comment will be made on a number of these cases.

CASE I.—A. M., aged forty-five years; cook in the staff kitchen. Patient had been complaining for two days before she made her illness known to a physician. Symptoms were vomiting, profuse bloody diarrhea; could retain no food in her stomach. All superficial reflexes were absent; there was pain along the course of the peripheral nerves. She entered into a state of coma on the sixth day of her disease, which was followed, in a few hours, by death.

Autopsy showed a marked congestion of the superficial veins along the greater curvature of the stomach, with areas of hemorrhage throughout the course of these veins. At the cardiac end of the stomach there was an area encircling the stomach, 2 cm. in width, presenting marked congestion and many small hemorrhages into the stomach. The intestines also showed an acute congestion throughout. The lower bowel, however, showed less evidence of congestion, but was spotted throughout its entire length by many petechial hemorrhages. The liver showed many areas of focal necrosis. The remaining viscera evinced nothing pathological.

CASE II.—R. K., aged fifty-two years; a patient helper in the staff kitchen; working with the above-described case in the morning. She was taken ill at about the same time with nausea; frequent evacuations of her bowels contained only mucus, with great prostration. There was marked tenderness over the superficial nerves of both upper and lower extremities. The patella and Achilles reflex, however, were present; abdominal and epigastric reflexes were absent. The temperature never went above 100°. The patient was unable to walk or use her arms. She continued in this condition for a month, when the clinical symptoms gradually disappeared, leaving her with a residual of an upper and lower peripheral palsy.

CASE III.—C. C., aged sixty-five years; the patient was taken sick suddenly with a temperature of 103.8°; vomiting; bloody mucous bowel movements. Her superficial reflexes of the lower extremity were absent. She could bear no weight on her feet nor allow the bed-clothes to touch her lower limbs. She became more and more prostrated and exhausted, and died on the twelfth day of her disease. The autopsy findings were the same as those described in Case I, with the lesions confined to the intestinal tract and liver.

CASE IV.—M. C., aged twenty-seven years. The patient became ill, with a temperature of 100°, associated with vomiting and profuse diarrhea of a blood-stained type. She was in the state of

collapse within a few hours after recognition of her disease. She then manifested a flaccid paralysis of the lower extremity, with a double foot-drop. All superficial reflexes were absent. There was marked tenderness over the peripheral nerve trunks and muscles of the lower extremity. During the first six days she showed rapid emaciation. On the eighth day of her disease her temperature dropped to 98°. On the ninth day her temperature rose to 101° and gradually increased, so that on the fifteenth day of the disease it was 105°, and was followed by death. The autopsy in this case showed marked injection of the vessels of the upper part of the small intestine.

Case V.—M. McC., aged fifty-six years; patient was taken sick with a temperature of 101.5°; the bowels were loose, containing shreds of mucus and traces of blood, which increased during the second and third day. Aside from absent patella and Achilles reflexes there was no evidence of a peripheral neuritis. Patient died on the eighth day of the disease. No autopsy.

Case VI.—M. C., aged sixty years; onset of the disease recognized by a temperature of 103.2°; vomiting; stools diarrheal, containing mucus and blood. Patella and Achilles reflexes absent, but no objective evidence of acute inflammatory peripheral neuritis. Death occurred on the fourteenth day. No autopsy.

Case VII.—K. H., aged fifty-seven years. Onset of the disease recognized by temperature of 102°; diarrheal bowel movements contained a large quantity of mucus. Patella and Achilles reflexes absent, but no other evidence of peripheral neuritis. She died on the ninth day. No autopsy.

Case VIII.—I. D., aged fifty-six years. Disease initiated by rise of temperature to 102°, associated with vomiting and diarrhea. She complained of marked headache, backache and cried out with pain in her feet and legs and said she could not use her arms or legs. She could not stand or walk. All reflexes were absent (superficial), in both upper and lower extremities. At the end of the first month she manifested only the residuals of a multiple neuritis. Her hands were clumsy, showing an inability to coördinate, especially in eating. (At the present time the patient is helpless, cannot walk; shows a double foot- and wrist-drop and is only able to do a few small duties with her hands.)

Case IX.—K. T., disease initiated with a rise of temperature to 100°, diarrhea and vomiting. She could not walk or stand; moved her limbs with great difficulty, as if they were stiff, and complained of nerve and muscle tenderness. The legs and feet were cold and markedly manifested venous congestion. The patella reflex and Achilles reflex were absent. Three weeks after the onset of the disease she showed a recovery, as far as its acute manifestations were concerned, but there was present marked incoördination in both upper and lower extremities. Two months after the onset of the

disease the patient showed complete recovery, with a disappearance of her double foot- and wrist-drop, but she maintained a loss of her superficial reflexes.

CASE X.—M. P., aged thirty-seven years. The disease began with vomiting; bloody diarrheal stools; marked prostration. She complained of severe headache and backache, with pains in her legs on pressure and marked tenderness along the peripheral nerves of both upper and lower extremities. All the superficial reflexes in both the upper and lower extremities were absent. The acute manifestations of the disease disappeared by the eighth day. The patient's convalescence was interrupted, with a complete recovery from her neurological symptoms.

CASE XI.—M. S., aged forty years. Patient's disease process was initiated by a temperature of 103.6°; nausea and vomiting; bloody diarrheal stools. These gastro-intestinal symptoms lasted fifteen days. During this time tenderness along the nerves and muscles in the lower extremities was manifest. The superficial reflexes of the lower extremity were greatly diminished. At the end of the twenty-first day the patient began to improve and her convalescence ended in a recovery of both the gastro-enteric and neurological symptom-complex.

CASE XII.—A. McG., aged thirty-six years. The disease began with a temperature of 103° and marked vomiting. The bowel disturbance, however, was slight. There was marked tenderness over the peripheral nerves of the lower extremities, with a loss of both patella and Achilles reflexes. The duration of the disease was eleven days, followed by a complete recovery.

CASE XIII.—C. H., aged sixty years. Initial temperature rise 104°, associated with a diarrhea that continued for seven weeks. There was marked tenderness over the peripheral nerves of the left lower extremity only. The patella reflexes were present on both sides, however. The Achilles also were present. The patient made a slow but gradual recovery.

CASE XIV.—M. G., aged thirty-eight years. No rise in temperature. Repeated attacks of vomiting. Bowels diarrheal in type, but no blood or mucus. He complained of great pain in the left leg. There was marked tenderness along the peripheral nerves of both extremities. The superficial reflexes of the lower extremities were absent and the left foot showed a distinct drop. This patient made a slow recovery.

CASE XV.—S. T., aged fifty-nine years. Onset of the disease manifested by a temperature of 100°. During the first three weeks of the patient's illness there was marked constipation. During the next few weeks there was an acute gastro-enteritis. During the entire disease process, however, the patient was very sick, complaining of a great deal of pain in the upper and lower extremities and the annoying symptom of frequent attacks of sneezing. During

the second week of the disease process the peripheral neuritis became complete, so that the patient had a well-marked double foot- and wrist-drop. The superficial reflexes in both the upper and lower extremities were absent. During the fifth week of the disease atrophy of the muscles of both the upper and lower extremities began to be manifest, which continued to a marked degree so that at the present time the patient is utterly helpless.

In the cases in question the sudden outbreak of an acute gastro-enteritis naturally leads one to the opinion that said infection must have been introduced *via* the gastro-intestinal tract. It therefore seemed plausible to obtain cultures from milk, which is one of the staple articles of diet in ward patients. Cultures from the milk as it came from the dairy were made and a rapidly growing staphylococci made its appearance in twelve hours. These cultures were grown on both plain and 3 per cent. glycerin media. Bacterial count was also made and found to contain several millions per cubic millimeter.

It therefore was assumed that a virulent, rapidly growing staphylococcus was introduced into the gastro-intestinal tract. Cultures were then made from the nose and throat and excreta. Here, again, rapidly growing colonies of staphylococci were obtained. It might be stated, however, that in several cases the pneumococci and streptococci were grown from the throat and nose cultures in the first twelve hours, but they were quickly overgrown by a staphylococci which finally outgrew the streptococci and pneumococci. Cultures obtained from the blood of several patients also showed a growth of staphylococcus at the end of eighteen hours. Here, again, in one case, at the end of twenty-four hours, the colony growth resembled, morphologically, the pneumococci. When regrown, however, upon transplantation, it assumed the characteristics of the staphylococci and grew out at the end of forty-eight hours as a pure culture of Staphylococcus aureus. Catheterized specimens of urine made with the same result in the majority of the cases examined, namely, a final growth of Staphylococcus aureus.

Up to this time one must conclude that the source of infection was milk; that the agent was the staphylococcus; that the mode of entrance was *via* the gastro-intestinal tract with an acute gastro-intestinal reaction, as manifested by the symptoms, vomiting, marked gastric pain and distress, with profuse bloody diarrhea. During this acute infective stage there was the concomitant rise in temperature and in some cases an acute delirium and excitement lasting over several hours. Thus far clinically and clinicopathologically the signs and symptoms are indicative of an acute infection of staphylococcus type.

The question was then raised: What relation did the neurological signs, which made themselves manifest within the first twenty-four hours, bear to this acute infection? Blood analyses as above noted

yielded the staphylococcus; therefore there must have been a staphylococcus bacteremia—a hematogenous infection.

Absorption from the intestinal tract as proved by experiments shows conclusively that derivatives of food products are transmitted directly to the blood capillaries, and that any interference with the lacteal circulation does not interfere with the absorption, especially of proteid products. Biologically, bacteria are of a protein make-up. Their absorption or transmission from the intestinal system to the vascular system would therefore undoubtedly occur through the capillaries and thus make an entrance into the general circulation. After entering the circulation the selective action of the bacteria, according to Rosenau, would take place and in the series of cases above reported it is evident that their activity was directed toward the peripheral nervous system, for somewhat coincident with the acute infection there developed symptoms and signs suggestive of a peripheral polyneuritis. Out of this series of cases there were four which came to autopsy, and where it would require prolonged discussion to review each case by itself the examiner will summarize his findings. The changes in the viscera and peripheral nervous system were much the same in all cases and they will therefore be described as a group.

Macroscopically the intestinal tract showed an acute hemorrhagic gastritis and enteritis, the mucous membranes being deeply injected and showing small hemorrhages throughout its mucous coat.

The liver in all 4 cases showed indications of retrogressive metamorphosis; 1 case showed an advanced fatty degeneration with focal necroses and the remaining 3 cases showed distinct focal necrotic areas. The fact that in all 4 cases coming to autopsy there were observed focal necroses of the liver would distinctly point toward the fact that there must have been an acute systemic infection, for it is hardly possible to believe that these retrogressive changes noted were merely coincident to the general disease processes.

Sections of the peripheral nerves and of the mid-dorsal cord showed small hemorrhages between the nerve bundles both in the nerve itself and in the nerve roots as attached to the cord. There were also noted extravasations of cells between the individual fibers. Examination of the anterior horns for a disturbance in the motor cells, keeping in mind anterior poliomyelitis, gave negative results, and there were no indications of a hemorrhagic process in the horn itself.

To recapitulate: It would appear in summing up the entire situation that (1) there was introduced into the body an exogenous toxin (staphylococcus infection); (2) that it was introduced into the gastro-intestinal system and there produced an acute infective gastro-intestinal; (3) that there was a transmission of the infective agent from the intestinal tract to the general circulation, producing a septicemia (staphylococcus in type); (4) that for reasons still to

be explained, but to be constantly kept before one's attention, this particular infection had a selective action upon the peripheral nervous system and caused the symptom-complex known as peripheral polyneuritis; (5) clinicopathologically the milk, throat cultures, blood, fecal examinations and urinary tests for bacteria showed in general the staphylococcus; (6) pathologically there was observed an acute hemorrhagic gastro-enteritis, multiple focal necroses of infectious origin in the liver and acute hemorrhagic neuritis (hemorrhages between the nerve bundles).

Therefore, clinically and pathologically, the diagnostic grouping of these cases has been placed in the acute infective enteritis group with a polyneuritic syndrome.

FUNCTIONAL BLOOD-PRESSURE.

By Robert Franklin Ives, M.D., F.A.C.P.,
NEW YORK.

In contradistinction to those permanent or organic changes in the circulatory apparatus which signify their presence by a constant or stationary sphygmomanometric reading, hypertensive in character, and about which medical opinion accepts the rising valuations as of supreme clinical importance, there must also be recognized, and properly evaluated, a larger group of variations, primarily functional in nature, and which, while at times hypertensive in reading, are due to disturbances of a functional or physiological character.

This first type is understood as being organic or permanent and the latter as functional or transient.

The first is pathological and therefore a factor for serious concern; the latter is still considered as within the elastic bounds of the physiological and must be so interpreted, and therefore kept from passing over into the domain of the pathological.

The vital and essential principle always to be recognized when considering the importance of blood tension lies in this fact—this great truth—that the etiological factors causing this rise in the blood tension within the bloodvessels, numerous and diverse though they be, act by causing an elevation of the blood tension or pressure primarily, and only secondarily do the more permanent or organized changes follow as a result of the irritation or disturbances being long continued.

In the understanding of functional blood-pressure disturbances, as well as the arteriosclerotic changes in the bloodvessels, the structural elements or anatomy of the bloodvessel wall must be kept in mind.

The walls of the arteries consists of three coats, which, named from their relative position, are the inner, the middle and the outer. The structure and relative thickness of these coats or tunics vary in vessels of large, medium and small caliber.

The media or muscular coat is the thickest coat of the artery and the one upon which attention is focussed. It consists of many circular lamellæ of involuntary muscle fibers, intermingled with connective tissue, in which elastic fibers are conspicuous. This muscle tissue gradually attenuates as the capillaries are approached, until finally, in the capillaries themselves, no muscular fibers appear, only nucleated endothelial cells. Finally, the capillaries, by their union, constitute the capillary plexus, *i. e.*, the retia capillaria.

As regards the innervation, it is well to recall that the sympathetic, through its vasoconstrictor and its vasodilator fibers, maintain vessel tonicity.

Luciani[1] states: "There are, accordingly, constrictor and dilator nerves to the bloodvessels, the former corresponding to the systolic and the latter to the diastolic nerves of the heart. Vascular rhythm and tonicity are analogous to cardiac rhythm and tonicity."

Foster[2] says: "We have repeatedly insisted that the relaxation of a muscular fiber is as much a complex vital process, and as truly the result of the muscular substance, as the contraction itself, and there is *a priori*, no reason why a nervous impulse should not govern the former as it does the latter."

From the vasomotor center, then, is the tonicity of the vessel controlled. Thus, any influence, metabolic, endocrinologic, toxic or psychic, may affect the musculature of the vessels with the production of constriction, and this constriction, through the development of the muscular overaction, may result in the condition of hypertonus.

Through the action of localized contractions in the great splanchnic areas there may be a pressure rise (functional hyperpressure) or a fall through splanchnic relaxation.

Our reasoning thus leads us to the belief that a prolonged influence of the vasomotor controlling mechanism, through the agencies of faulty metabolism, etc., or by the production of overdevelopment of the muscular tissue in the walls of the arteries, with the resultant hypertonus, may also be at the foundation of the functional hypertensive blood-pressure.

Degeneration in the walls of the bloodvessels may develop without the production of a raised blood-pressure, but where it becomes a factor of danger, and of serious concern to the circulatory balance, it always follows this period of functional or physiological rise instead of preceding the same. Therefore, the fundamental feature for correction, and the great clinical value of this question

[1] Human Physiology, vol. i, p. 343.
[2] Text-book of Physiology, Part 1, p. 313, 5th ed., 1888.

of blood-pressure, are to be found in this early knowledge of the disturbing elements in the blood stream, acting in the twofold relation of causing a primary elevation of pressure and associatedly a structural though an insidious change in the vessels themselves. As mentioned, these arterial changes and sclerotic lesions may develop in the peripheral vessels in the aging and aged even to the formation of calcareous plaques, as noted in the senile or decrescent type of arteriosclerosis described by Clifford Allbutt, without causing a manifest elevation in the arterial pressure. In contradistinction to this fact it may also be noted that a permanent hypertensive reading is frequently observed in persons about the fourth or fifth decade, in whom no outward evidence of arterial sclerosis can be discovered, though positive changes have taken place in the cerebral or splanchnic vessels. This condition has likewise been fully described by Allbutt and called hyperpiesis. Reference will be made to this condition later.

Between the great group of diffuse arteriosclerosis, chronic Bright's and hyperpiesis, with permanent organic and fixed hypertension and the great group of normal cases, so called because it is necessary to have an approximate standard even though the normal limit of flexibility may be greater than at present accepted, there lie two groups of functional blood-pressure conditions which may be termed:

1. Functional hypertensive blood-pressure cases.
2. Functional hypotensive blood-pressure cases.

A consideration of these two groups may be of value.

1. Functional Hypertensive Blood-pressure. Our increasing knowledge of the dynamics of the circulation discloses the fact that pressure or tension, high or low, in the vessels are registered by the mercury manometer, and as recognized clinically, is a condition of functional variation which may affect the individual at all ages and under various circumstances of life. For instance, changes or variations may be brought about at different hours of the day; it may be influenced by the mental attitude or the type of diet and by emotion, especially anger, particularly when suppressed through ideas of dignity. This may so elevate the tension as to cause bronchial wheezing, and an asthmatic cough, especially where the tonicity of the cardiac musculature is subnormal. Strenuous exercise will raise while rest will lower the arterial tension.

Normal blood-pressure, it may be mentioned, is dependent upon a properly functionating vasomotor system; upon the integrity, strength and energy of the cardiac musculature; upon the normal elasticity of the arterial walls; upon the volume of the circulatory blood—its viscosity—and upon the peripheral resistance. Thus, anything that disturbs the physiological harmony of this mechanism will naturally influence or alter the mechanical agencies of its flow and so register a change in the blood-pressure or tension. Attention

has rightfully been called to the fact, by many authors, that this recorded pressure or tension is classed as a symptom and not as a disease. As a symptom it proves of inestimable value in the study of disease. It thus aids in the differential between the organic and the functional lesions.

Realizing, then, these functional variations in the manometric reading it is advisable to repeat the observations a number of times, and on different occasions, when making a study of hypertension. Take the pressure after eating, after exercise, and after a prolonged rest. It may be advisable for the observed patient to remain recumbent for a period of twenty-four hours, with strict attention to the diet, and with full intestinal elimination, before the final judgment is rendered.

If the case is functional, a marked reduction in hypertension is witnessed; if organic, no marked change results.

Etiology. It may well be asked and answered: What are the usual causes for heightened pressure? Usually due to errors of diet, eating and, previous to the advent of prohibition, drinking, long continued; combined with a life of worry, mental depression and emotion. In the largest number of cases, disturbances in metabolism, by which is inferred those forms of destructive metabolism whereby faulty end-products of digestion, toxic to the living somatic cells and vasomotor center, maintain a constant pressor effect, through irritation, with the eventual development of the productive changes in the cells themselves. Many persons observe little judgment in their gastronomic seances, with the resultant overwhelming of the system by the toxic products developed. Intestinal stasis, from whatever cause, with biliary deficiency, hasten the production and the absorption of these putrefactive toxic products.

Auto-intoxication. This resultant of the abnormal or destructive metabolism undoubtedly lies at the foundation of the hypertensive and arteriosclerotic alterations. Intense is the discussion surrounding this subject, and intensive are the efforts of the chemicophysical laboratories to fathom it.

Dr. Louis Faugeres Bishop,[3] in seeking to solve the "riddle of arteriosclerosis," develops a convincing case against auto-intoxication. To quote: "I believe (the key) is to be found in the still obscure field of biochemistry, and I believe in the end it will be discovered that the reason for the perfectly apparent increase of arteriosclerosis of modern time is to be found in the well-known changes with regard to the habit of people in connection with protein food and the different manner in which they are handled commercially, together with some factor or factors, yet to be analyzed, that render food idiosyncrasies of a low grade producing unconscious poisoning."

[3] Arteriosclerosis, 1915, p. 15.

Professor Victor C. Vaughan[4] discusses this problem from the standpoint of individual protein sensitization and anaphylaxis. He states from laboratory experience, "The protein poison is a powerful agent," acting against the vital somatic cells.

Luciani[5] quotes, as the result of the action of intestinal bacteria in their transforming action on the carbohydrates, fats and proteins, the following:

"On carbohydrates: By fermentation, the production of alcohol, lactic, benzoic, succinic, butyric and valerianic acids; also carbonic acid gas, methane or marsh gas and hydrogen gas.

"On fats: The production of glycerol and fatty acids.

"On proteins: The toxic putrefactive elements: proteoses, peptones and amino-acids. These amino-acids are very complex and subtle agents for good or for evil."

According to Lusk:[6] "One must know the life of sixteen amino-acids in order to be familiar with the metabolism of protein." These nitrogenous bodies, indol, scatol, phenol, pancresol, phenyl-propionic acid, etc., are toxic agents of very great moment. In addition, a group of chemical compounds, the so-called ptomains, appear; these little-known alkaloids are powerful agents of destruction."

With such in mind it is evident that if these products of putrefactive activity and metabolic decomposition acted suddenly they would very quickly overwhelm the vital resisting forces of the human organism. Therefore, when acting, in cases of intestinal stasis, very gradually and over long periods—decades—they produce the changes in arterial compensation and degeneration, with the production of this primary functional, and eventually a permanent or organic blood-pressure variation.

This is what is intended by the term destructive metabolism.

Other Causes: Endocrine disturbances, especially of the thyroid, with the association of hyperthyroidism, when long active, gradually produces an overacting heart; with the development of hypertrophic changes in both the cardiac musculature and the musculature of the walls of the arteries.

Blood-pressure observations, by calling attention to this state, may spare the organism from the terminal apoplexy or cardiac exhaustion.

Infectious Agents: The ubiquitous microbe, the bacterial organism and their toxic products undoubtedly act to the detriment of the somatic cells. Undiscovered areas of focal infection must be credited as etiological agents.

Syphilis and the metallic poison, etc., add to the list.

The hypertension of nephritis is assumed to be organic. Little

[4] Am. Jour. Med. Sc., February, 1913.
[5] Human Physiology, vol. iii.
[6] The Science of Nutrition, 3d ed., p. 175.

attention, therefore, is given to it under the heading of functional hypertension; still:

The etiology of this large class is unsettled, for while there are many theories the only one thoroughly confirmed is that of Janeway, Carrel, Sampson and Pearce, who proved that the reduction of the amount of kidney substance alone may cause hypertension.

Attention is directed to the fact that the early changes may to a degree be assumed to be functional. Thus the early use of the manometer would prove a safeguard against neglect or oversight and the ultimate evils attendant upon a true nephritis.

Hyperpiesis: Vitally important is it, in cases showing signs of high pressure, to early assign the condition to its rightful category. A class of cases very frequently met with during these days of strenuousness is the one so fully described by Clifford Allbutt, regius professor of physic in the University of Cambridge, England, and called by him hyperpiesis. It seems to be little understood by the profession at large. Allbutt defined this condition as a state or disease whose essential feature and earliest manifestation is hyperpiesis or elevated blood-pressure. Its causes probably fall within the category of etiological factors given. At first the response to the irritations causing the heightened pressure is wholly functional, but in the course of time, the causative factors still acting, it is followed by the cardiac hypertrophy and by the arterial sclerosis. It then is classed in the list of the organic high-pressure cases. My reason for introducing it here is to call attention to the undoubted fact *that early in its history it comes under the functional high-pressure classification, and so merits attention.*

Houchard calls this early period "the presclerotic state."

Clifford Allbutt states emphatically:[7] "If we catch hyperpiesis early, and keep at work against it, it can be cured more often than not." Occurring in people of apparent robust health, it progresses insidiously months and years before it is suspected. Only by the regular use of the sphygmomanometer can it be detected early. When the first symptoms of dyspnea, from the breaking down of the heart's reserve force, appear, or the presence of precordial or substernal oppression or pain is experienced, or a sudden attack of pulmonary edema upon exertion or symptoms referable to the cerebral vessels, *i. e.*, slight shock or warnings from vasomotor spasms, result, the process is well advanced.

A period of increasing nervousness, irritability or consciousness of the burden entailed in holding one's position in life, and a similar consciousness of a lessened ability to meet the same with undue fatigue, these register clinically the earliest signs and bespeak for recognition and a successful therapy. Thus: suspect the tendency to, or the presence of, hyperpiesis in every full-blooded, stocky man

[7] Diseases of the Arteries, Including Angina Pectoris, vol. ii, p. 81.

or woman of plethoric habits, active temperament and with hearty appetites at the period of the late middle life, between the ages of forty-five and fifty-five years.

Climacteric Hypertension. So deeply impressed is the profession with the thought that hypertension is synonymous with nephritis, and that even hyperpiesis must always be, to a degree, allied to chronic Bright's, that there hardly seems room in their thoughts for this essential truth about pressure: that functional hypertension can occur in many and diverse conditions.

I wish also to suggest that there is a type of high pressure frequently found in women at the period of the menopause. These cases do not show any evidence of arteriosclerosis and no obtainable evidence of nephritis, either in the blood or in the urine. The retinal picture is likewise normal. To this class, then, the term hyperpiesis hardly seems correct, because they develop during or subsequent to and are apparently closely associated with that complex function of ovulation and ovarian glandular secretion, with their influence over all bodily functions.

During this period of ovarian dysfunction, and especially following its cessation, these patients develop a group of unassociated symptoms, nervous, gastric and cardiac in origin, which cause them to seek relief. As a rule, they are healthy in appearance, rather obese, though not necessarily so; are active, nervous and inclined to worry. They are met with between the years of forty and fifty years. They have headache, vertigo, paresthesias, epistaxis, numbness or sleeping of the extremities. On examination they show a high arterial blood-pressure, usually about systolic 200 and diastolic 120 mm. Hg.

Under rest, diet, bromide sedation and endocrine medication a very pronounced drop in the pressure is obtained, to their very great relief.

Arthur H. Hopkins[8] has described a group of these cases. The condition might be more fully elaborated. Attention is directed to it for the purpose of classifying it among the functional pressures and to suggest that a routine blood-pressure examination be made in all women at the menopause seeking relief from the obscure symptoms enumerated above.

Do not call these cases hyperpiesis, rather climacteric high-pressure cases.

Functional High Pressure in Obstetrics. To the obstetrician the knowledge of functional blood-pressure is of the highest importance. The response of the arterial controlling mechanism to the toxins developed during pregnancy causes a hypertonic rise, which at once suggests the advent of a toxemia and foreshadows the advent of the dreaded eclampsia.

[8] Am. Jour. Med. Sc., June, 1919, p. 826.

It is well to recall that the normal blood-pressure in a normal healthy pregnant woman will average close to 118 mm. Hg, with a gradual increase in the later months.

During the early months of the pregnancy, with nausea and vomiting, the toxemia or endocrine imbalance may cause the pressure to fall a few points, especially in severe cases. My experience seems to warrant the belief that feeding these patients with ovarian glandular substance restores this fall.

But, and here is the factor of real importance: To every physician who cares for maternity cases it should be known that a high 150 to 160 mm. Hg reading and a rising pressure in the latter half of pregnancy, and especially so when associated with albuminuria, constitute, very often, the earliest signs of a toxemia, which may suddenly terminate in eclampsia.

This hypertensive blood-pressure is purely functional, for following the birth of the child, in eclampsia, usually within forty-eight to seventy-six hours the pressure will fall to figures approximating normal. Therefore, as far as it is possible to outline suggestions in maternity cases, the following is suggested:

Invariably, upon the acceptance of a maternity case, obtain the blood-pressure data and record the same. Throughout the early periods verify the findings monthly. In the latter half of the pregnancy a blood-pressure below 124 mm. Hg may be disregarded. A pressure reading, however, from 125 mm. to 150 mm. Hg needs very careful watching. A pressure over 150 mm. Hg, when the original normal pressure was about 120, is considered fraught with danger and needs very careful eliminative measures; and should it show a tendency to rise higher the induction of premature labor should be considered.

The role, therefore, of the sphygmomanometer in pregnancy is a very important one. As a corollary to the above, after delivery, in involved cases, the persistence of the high pressure must always be considered of moment and the case watched and treated until it falls to normal.

The modern scientific care of maternity cases, therefore, includes the routine use of the manometer, with a view to the recognition of the functional elevations proved of such supreme importance.

Hypertension in Cerebral Hemorrhage. In apoplexy the cerebral hemorrhage always causes a marked functional use to heights greater than the previously registered heights maintained by the organic causative factor. A recent case with original systolic pressure of 225 mm. Hg, diastolic 115 mm. Hg, prior to the hemorrhage, rose within one-half hour to the high figure of 285 mm. Hg systolic and 150 mm. Hg diastolic The resulting coma continued until the pressure gradually fell to 230 mm. Hg systolic and to 130 mm. Hg diastolic, when consciousness returned.

Hypertension in Typhoid Fever. In the course of typhoid fever the pressure is liable to decline below the normal readings for the patient in health. A sharp rise in the blood-pressure accompanied by abdominal pain suggests perforation of the intestinal wall.

Hypertension in Cerebral Growth. A rising pressure is usually associated functionally with the headache, vomiting and papilledema of cerebral growths. Removal of the growth lowers the pressure.

2. The Functional Hypotensive Blood-pressure Cases. A very important group of cases showing hypotensive or depressive readings are frequent claimants for medical consideration. This condition, while not as spectacular as the hypertensive group, is no less important, and merits intensive study for its proper differentiation and treatment.

The condition is often associated in the minds of the physicians, and even of the patients themselves, with the idea of cardiac exhaustion; but while the inherent cardiac musculature may not be fully normal and is usually subnormal, still the lowered tone so evident is more likely due to deficiency of the vasomotor function from whatever constitutional cause. Constitutionality, then, is very evident in these subjects.

It is essential to remember, however, that a low arterial pressure may be practically normal for a particular individual, and it by no means follows that the arterial pressure is abnormal, because it is below the average level of pressure generally present in a healthy subject of the same age.

Cases are seen in early and middle life enjoying health and doing their work, in whom the arterial pressure has not exceeded 90 mm. Hg systolic and 60 mm. Hg diastolic. A very recent pregnant woman of twenty-four years showed a systolic reading of 85 mm. Hg and a diastolic reading of 50 mm. Hg. No complaint except indisposition to exertion was made. While this latter borders on the abnormal and prompted measures for its improvement, it is cited as evidence of the elasticity of the normal limits of pressure.

A hypotensive pressure must be considered functionally pathological, however, when conjoined with signs and symptoms of impaired health and sense of well-being.

Hypotensive cases may be separated into several groups:

1. The Tuberculous Group. Constitutional deficiency, through direct tuberculous inheritance, is a profound factor in depressive conditions.

Tuberculosis affects the vitality of the whole organism, hence the low readings. It is well, therefore, to always suspect a tuberculosis, active or latent, in those cases of young men and young women between the ages of sixteen and twenty-six years who, while showing wasting and anemia, have an associated hypotension.

2. Endocrine Deficiency:
   A. Toxemic group.
   B. Pituitary group.

A. *The Toxemic Group.* Recent studies of the dominance of the endocrine glands over the physical functions and the vasomotor balance have awakened intense interest in this specific group. This class of patients show no evidence of tuberculosis, look normal to casual observation, but suffer with a depression of their vital functions termed asthenia. They lack "pep," are easily tired and have no reserve. By force of will they may rise to the occasion for the time, but readily revert to the expressed state of fatigue. They are especially met with among young women who are relegated to the class of neurasthenics for the want of a better comprehension of their ailment. At the present time it is realized that asthenia or neuromuscular depression, with its hypotension, is really a condition of cellular intoxication. According to Henry Harrower, "If the regulating mechanism that controls the circulation, cardiac efficiency and blood-pressure is insufficient, then asthenia must result from the accumulation of the ordinary amounts of cellular waste." The chief cause of this group, with its asthenia, appears to be due to a condition of chronic toxemia from faulty oxidation and deficient elimination.

By the use of the products of glandular substances from the adrenal body, with its synergist the thyroid, augmented by lecithin elements a marked restoration of the proper functioning of these bodily organs lessens the asthenia and raises the pressure by the activating effect upon the vital functions themselves.

So marked is the benefit derived by this class of hypotensive cases that efforts should be made to recognize this type among the depressive groups. Whether or not adrenalin acts, *per se*, to raise blood-pressure the present opinion seems opposed to the theory. Experience, however, does show that the use of the suprarenal glandular substance, aided by other therapeutic measures, does so act on the psychonervous functions as to sustain them and eventually cause a restoration to more normal conditions.

B. *The Pituitary Group.* Again: Must deficiency of the endocrine elements be recognized as a provocation of not only low blood-pressure but also of a low constitutional state itself?

Dr. Walter Timme[9] describes a series of cases observed at the Neurological Institute of New York City, undoubtedly due to pituitary deficiency. These cases are constantly seen in practice, are not recognized, and are wrongly diagnosed and wrongly treated. They all suffer from some psychosis associated with their bodily deficiency. Timme refers to the condition as "A new pleuriglandular compensating syndrome."

[9] Medical Clinics of North America, January, 1919.

They show symptoms of intratemporal headache, great fatigability, low blood-pressure (hypotension), skeletal growth abnormalities and usually sex deficiences.

They are seen in both early, middle and late stages, or from adolescence to middle life.

This syndrome seems to involve the thymus, adrenal, thyroid, gonads and pituitary bodies.

Beginning in early life through a failure of the thymus function a necessary compensatory development of the other glandular bodies is imperative for the continuance of the organism. Seen first in youth some years before or after puberty it continues actively for a period of about twenty years.

The first symptoms are those of the thymicolymphatic state observed between the years of ten and fifteen. The second or compensatory pituitary state of puberty between ten and twenty; the pituitary gigantism state between twenty and thirty; and finally the developed state of acromegaly.

Low pressure is incident to all stages.

The functional character of this complex condition is evidenced by the marked general improvement following the feeding of these patients with pituitary gland products, a corresponding rise in the blood-pressure indicating the functional hypotensive nature of the vasomotor condition.

3. *Infectious.* Bacterial invasion of the body functionally depresses the vital activities, both by their presence and by the developed toxins. Influenza, pneumonia, diphtheria, typhoid, etc., are all associated with depressive readings. So profound may be the depression as to quickly overwhelm the organism.

Convalescence should be guided by the manometer in order to direct the activities of the patient.

4. Shock, hemorrhage, vomiting and diarrhea account for many low readings, the correction of the cause restoring the pressure.

5. With a view to the above outlined conditions it is evident that the functional aspect of the question of blood-pressure is a very important one, to be given consideration in every case of hypertension and hypotension before assigning the causative condition to that of the organic or permanent type; and that it is during the period of this functional development that therapeusis and associated methods of treatment warrant the expectation of success. Efficient treatment is dependent upon accurate diagnosis: To differentiate therefore, between the functional and the organic disturbances is the *sine qua non* of success.

A STUDY OF THE BLOOD AFTER SPLENECTOMY: WITH SPECIAL REFERENCE TO THE LEUKOCYTES.

By Milton W. Hall, Major, M.C.,
U. S. ARMY.

(From the Department Laboratory, Southern Department, U. S. Army.)

Shortly before noon, July 28, 1919, a cavalryman at Fort Sam Houston, Texas, while caring for his horse after the usual drill, was seized with faintness, nausea and sudden sharp pain in the left upper quadrant of the abdomen. He was brought to the Base Hospital in a condition of collapse. A definite diagnosis was impossible, but six hours after the onset of symptoms a laparotomy was done, with the tentative diagnosis of a ruptured viscus. Hemorrhage in the peritoneum was traced to a small tear in the spleen and the organ was removed. The temperature was subnormal on admission, and except for a short time on the following day was never above 100°. The wound healed promptly and without infection. After the first few weeks the patient appeared completely restored to health, though at times a moderate tachycardia was noted. He stated that he weighed more than ever before. The Wassermann reaction was negative, and before his discharge repeated examinations failed to reveal any abnormalities.

In most previous reports on the blood picture after splenectomy the emphasis has been laid on the changes in the red cells and hemoglobin, although far more striking changes, both quantitatively and qualitatively, have been recorded for the leukocytes. In the present case the anemia usually noted in man and in experimental animals was of such slight degree, if present at all, that attention was concentrated on the white cells almost exclusively.

In the nature of the case it was impossible to obtain a preliminary count that would represent the condition previous to the injury. After injury, but before operation, two counts showed respectively 25,250 and 15,250 white cells, with 83 per cent. neutrophiles, 15 per cent. lymphocytes and 2 per cent. endothelial cells. As this was during the presence of free blood in the peritoneum, with consequent absorption of fibrin ferment and slight fever, these counts are best disregarded in the present study. At each examination a total and differential count of the leukocytes was made. For the latter a sufficient number of cells was counted each time to ensure satisfactory check results. This was usually 400 cells, but when the count ran unevenly or differed markedly from those preceding as many as 1000 cells were counted. The usual classification of cells has been adhered to, except that the large mononuclear and transitional cells have been placed in one group as endothelial cells.[1] During the

[1] McJunkin, F. A.: Am. Jour. Anat., 1919, xxv, 27.

earlier part of the work the counts were made from films stained with Wright's stain, but as the fact became apparent that the endothelial cells were consistently increased, check stains were made with the alpha-naphthol stain of McJunkin.[2]

The counts were, as far as possible, taken at the same hour each day, from four to five hours after the comparatively light breakfast of the hospital wards.

In addition to the differential count the neutrophiles were classified according to Arneth's method. For facility in the comparison of results the sum of the numbers of cells in each hundred falling in groups 3, 4 and 5, that is, the more mature cells, is tabulated as the Arneth index.

The "normal" figures shown in the tables for comparison were obtained by averaging the figures given in five standard text-books. From these we conclude that the normal white count is one of 8000 cells, of which 5440, or 68 per cent., are polynuclear neutrophiles, 1920, or 24 per cent. lymphocytes, 400, or 5 per cent. endothelial cells, 200, or 2.5 per cent. eosinophiles, and 40, or 0.5 per cent. basophiles.

The Red Cells. The red cells have shown no notable change throughout. The slight reduction noted was perhaps not more than is accounted for by the hemorrhage found. A progressive increase in the red count was noted during the period of observation. The hemoglobin was recorded only in the later counts, as only then was a reliable instrument available. The final count showed 5,200,000 reds and 92 per cent. hemoglobin. Normoblasts were noted in two films, but not more than two were found in a specimen. No other abnormalities were seen. The fragility was not tested.

The White Cells. A glance at the charts showing graphically the changes in the white blood cells (Charts I, II and III) impresses one at first with the irregularity and variability of the counts both total and differential. More careful study, however, shows that the observations may be divided into three periods: a first, comprising the first nine observations and covering the period from the seventh to the sixteenth day after the operation, a prolonged intermediate period, and a final period embodying ten observations extending from October 15 to November 5, at which time the study ended. The first and last periods show fairly consistently uniform results. The intermediate period is one of great irregularity and sudden change in the picture.

During the first period the total white count was consistently high, varying from 14,600 to 19,800, with an average of 17,000. The differential counts, too, as shown in Chart II, did not vary more than is to be expected in successive counts on a normal individual. The average differential for the period was: neutrophiles,

[2] Arch. Int. Med., 1918, xxii, 157.

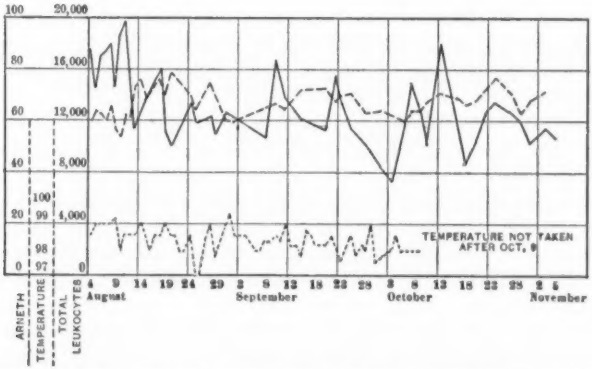

CHART I.—Total leukocyte count, Arneth index and temperature. Solid line, total leukocytes; broken line, Arneth index; dotted line, temperature.

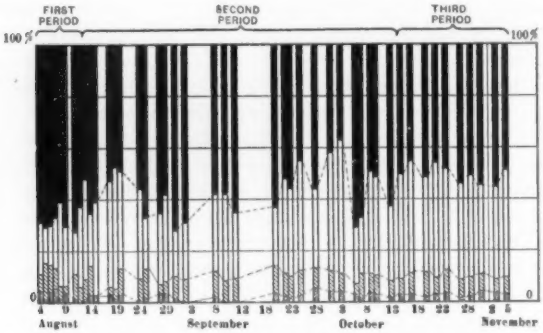

CHART II.—The differential count. Black, neutrophiles; white, lymphocytes; diagonal lines, endothelial cells; horizontal lines, eosinophiles and basophiles together.

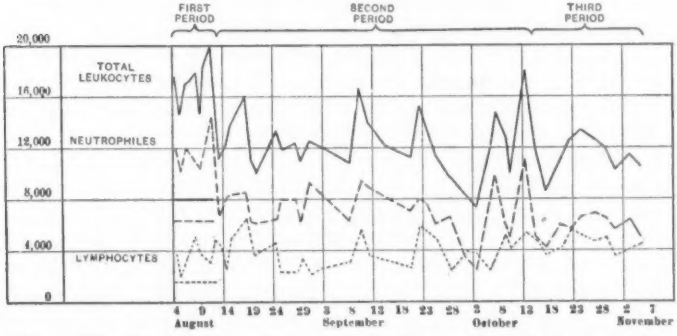

CHART III.—The actual numbers of neutrophiles and lymphocytes per cubic millimeter. Calculated from the total count and the percentage of each cell. Solid line, total leukocytes; broken line, neutrophiles; dotted line, lymphocytes. The short horizontal lines at the left end of the chart show the normal averages in each case.

68 per cent.; lymphocytes, 21.5 per cent.; endothelial cells, 8 per cent.; eosinophiles and basophiles together 2.5 per cent. With the exception, then, of a very small decrease in the lymphocyte percentage, with a corresponding increase in that of the endothelial cells, the differential relations are strictly normal, though the total count is more than twice the normal. Table II shows the number of each type of cell present and the ratio to normal in each case. The outstanding characteristic of this period would appear to be an increase to more than twice normal of the total number of leukocytes, with normal differential relations. During this period, too, the Arneth index approximated the normal.

The second period is characterized by such great variability that the computation of averages would be meaningless. The usual count was slightly above 12,000, but five times it went above 15,000, once reaching 18,000, and once for several days it fell to 8400 and 7400. The differential counts were equally bizarre. The neutrophile percentage varied between 72 and 37. Sometimes a sharp increase in total count was due to an influx of neutrophiles, but on at least two occasions (Chart III, August 18 and September 24) the rise was due mainly to a wave of lymphocytes. During this period the endothelial cells were consistently increased both relatively and absolutely.

In the third period the total count was still increased, but showed much more uniformity. The average was 11,570, or nearly once and a half the accepted normal. The extremes were 13,500 and 8700. The differential count showed still less variation than the total and is markedly changed from normal figures. The neutrophiles averaged 50.5 per cent., the lymphocytes 39.5 per cent., the endothelials, 7.8 per cent.; the eosinophiles and basophiles together, 2.2 per cent. Thus in spite of the increased total the actual number of neutrophiles present, as shown in Table II, and Chart III, is not above normal, and the increase in cells is due entirely to the mononuclear elements.

The average Arneth count on normal individuals, expressed in the way here used, is between 55 and 60. During the first period, then, the average index, 60.5, was not far from normal. With the beginning of the second period the index rose rather abruptly coincidently with a drop in the number of neutrophiles. According to the current conception of the cycle of development of the neutrophile this must mean a sudden cessation of production of this type of cell. However, subsequent increases in the number of neutrophiles were not accompanied by drops in the index, but rather the reverse obtained, a high point in the index tending to coincide with an increase in neutrophile count. During the concluding period the index remained well above normal, averaging 69. These relations are shown in Chart I.

TABLE I.—TABULATION OF BLOOD FINDINGS.

Date.	Red cells.	Hemoglobin.	Leukocytes.	Neutrophiles.	Lymphocytes.	Endothelial.	Eosinophile.	Mast cells.	Arneth index.
Aug. 4	4,320,000	....	17,500	69.0	20.0	7.0	4.0	0.0	60
5	....	....	14,600	71.0	13.5	14.0	2.0	0.5	64
6	....	....	17,000	70.5	15.0	12.5	4.0	0.0	62
7	4,370,000	....	17,300	67.0	20.0	6.0	5.0	0.0	59
8	....	....	17,900	61.0	33.0	5.0	1.0	0.0	66
9	....	....	14,800	70.0	24.0	3.0	2.0	1.0	57
10	....	....	18,600	....	....	....	...	...	54
11	4,460,000	....	19,800	73.0	16.0	10.0	0.0	1.0	62
12	....	....	15,500	63.0	31.0	6.0	0.0	0.0	61
13	....	....	11,200	52.0	39.0	8.0	1.0	0.0	73
14	....	....	12,300	66.0	20.0	12.0	0.0	2.0	76
15	....	....	13,700	61.0	37.0	0.0	0.0	2.0	67
18	4,650,000	....	16,000	53.0	41.0	4.0	1.0	1.0	76
19	....	....	11,000	47.5	47.0	4.5	0.0	1.0	70
20	....	....	10,200	49.0	38.0	11.0	1.5	0.5	79
24	....	....	13,300	56.0	35.0	9.0	0.0	0.0	70
25	4,460,000	....	11,900	67.0	29.0	12.0	1.0	0.0	64
28	....	....	12,300	65.0	28.0	4.0	3.0	0.0	74
29	....	....	10,900	58.0	34.0	5.0	1.5	1.5	69
31	....	....	12,600	72.0	18.0	9.0	0.0	1.0	60
Sept. 2	....	....	12,300	69.0	22.0	9.0	0.0	0.0	60
8	....	....	10,900	58.0	30.0	10.0	1.0	1.0	66
10	....	....	16,600	58.0	34.0	8.0	2.0	0.0	67
12	5,100,000	....	13,800	65.0	26.0	9.0	0.0	0.0	65
15	....	....	12,100	....	....	....	...	...	72
20	4,970,000	....	11,300	63.0	27.0	11.0	1.0	2.0	73
22	....	....	15,300	52.0	37.0	9.0	1.0	1.0	68
23	....	....	13,500	56.0	34.0	9.0	0.5	0.5	70
25	....	....	11,300	45.0	43.0	9.5	1.0	1.5	71
28	....	....	10,100	56.0	26.0	13.5	2.5	2.0	63
Oct. 1	4,930,000	....	8,400	42.0	46.0	9.0	1.0	2.0	64
3	....	....	7,400	37.0	52.0	8.0	1.0	2.0	63
6	....	....	12,000	70.5	22.5	4.5	2.0	0.5	60
7	....	....	14,800	66.5	22.5	9.5	0.5	1.0	64
9	....	....	12,800	49.0	40.0	8.0	2.0	1.0	64
10	....	....	10,200	50.0	40.0	8.0	2.0	0.0	67
13	....	....	18,000	62.0	29.0	7.5	0.5	0.0	71
15	4,600,000	90	12,000	51.0	39.0	7.0	1.5	0.5	69
17	....	....	8,700	45.5	43.0	9.0	2.0	0.5	66
20	....	....	11,000	51.5	37.0	10.0	1.5	0.0	68
22	....	....	12,600	45.5	45.0	7.0	2.0	0.5	
24	5,200,000	90	13,500	48.0	40.0	9.5	1.5	1.0	77
27	....	....	12,700	54.0	37.5	8.0	0.5	0.0	71
29	5,200,000	92	12,000	51.0	40.0	8.0	0.5	0.5	63
31	....	....	10,300	55.0	35.0	6.5	2.0	1.5	68
Nov. 3	....	....	11,500	55.5	36.0	6.0	2.0	0.5	71
5	....	....	10,700	49.0	42.5	7.0	1.0	0.5	

The effects of splenectomy in the dog have been exhaustively presented by Pearce, Krumbhaar and Frazier[3] in a recent monograph giving the results of their experimental work and a review of the literature of the subject. The removal of the dog's spleen produces constantly an immediate leukocytosis, mainly of the polynuclear variety, lasting for some months. There is relative

[3] The Spleen and Anemia, Clinical and Experimental Studies, Lippincott, Phila.

diminution of the lymphocytes and increase of the endothelial cells. In a majority of the dogs the eosinophiles were markedly affected, being largely increased either early or late in the course, and in some there was, for several weeks before the increase, a total absence of these cells.

TABLE II.

	Normal.	First period.		Third period.	
		Cells.	Ratio to normal.	Cells.	Ratio to normal.
Total leukocytes	8000	17,000	2.12	11,570	1.45
Neutrophiles .	5440	11,500	2.11	5,845	1.07
Lymphocytes .	1920	3,655	1.90	4,570	2.38
Endothelial cells	400	1,275	3.18	987	2.02
Eosinophiles . Basophiles .	240	510	2.12	255	1.06

The actual number of each variety of leukocyte, and the relation of each to the normal.

TABLE III.

	Normal.	First period.	Third period.
Neutrophiles	68.0	68.0	50.55
Lymphocytes	24.0	21.5	39.50
Endothelial cells	5.0	7.5	7.75
Eosinophiles	2.5	2.5	1.5
Basophiles	0.5	0.5	0.7

Comparison with normal of average differential counts of the first and last periods.

The recorded studies on the human are few and often conflicting. The reason for the discrepancies appears in the charts here shown, as from them it is easily possible to select a series of counts at fairly short intervals for a long period that would show almost any given picture with uniformity. The ideal case for this kind of work should show the removal of the organ for some small lesion that does not affect the structure or function of the mass of the organ, or for injury with only slight hemorrhage. For ideal conditions, too, a preliminary count should be made not only before operation but before injury in the latter class of cases. Moreover, as these figures clearly show, no conclusions can be safely drawn unless the counts are made at short intervals.

The cases that fulfil these requirements are very few indeed. Practically all reports show an immediate increase in the total white count, but the differential relations vary considerably. Some (Nicholas and Dumonhim,[4] and Meyer[5]) report lymphocytosis. Heaton[6] found a large increase in the large mononuclear and transitional forms. Musser[7] found the increase due mainly to polynuclear

[4] Jour. de physiol. et de path. gén., 1903, v, 1073.
[5] Jour. Am. Med. Assn., 1901, lii, 1231.
[6] British Med. Jour., 1911, lxxix, 501.
[7] Am. Jour. Med. Sc., 1911, cxlii, 501.

elements. Others (Nicholas and Dumonhim,[8] and Darling[9]) mention eosinophilia. Giffin[10] reports a case of splenomegaly in which the removal of the organ resulted in an enormous increase of eosinophiles, already numerous, and notes that these cells were of a more mature type than usual. The only reference to the Arneth index after splenectomy that I have been able to find referred to the condition after extirpation for pernicious anemia (Lee, Minot and Vincent[11]). In these cases the index, characteristically high in this disease (shifted to the right), returned toward normal.

In presenting these results it is recognized that the lack of a count before rupture detracts from their value, However, the subject had been in active military service as a cavalryman for over two years previously; his recovery was complete and the organ removed showed no abnormality other than the slight tear causing the bleeding. We seem justified in assuming the removal of a normal spleen from a normal man. The immediate effects of the operative procedure on the leukocytes should have passed when the counts were begun.

The results in this case may be summarized as follows: The moderate anemia present at the outset showed progressive improvement. The observations on the leukocytes may be divided into three periods: a first, characterized by a high count with all types of cell increased in practically normal proportion and a very slightly raised Arneth index; a second, showing great variability in total and differential counts and a varying but usually high Arneth; and a final period. in which the blood would appear to have attained to something approaching an equilibrium, and shows still some increase in the total count, but with the differential relations so altered that the increased total is seen to be due entirely to the presence of larger numbers of the lymphocytes and endothelial cells, while the granular leukocytes are present in normal numbers only. During this period the Arneth index remained consistently high.

It is perhaps permissible to suggest that the first period represents the effect on the organs of blood formation and destruction, of the removal of the spleen; the second period, lasting about two months, one of adjustment of the organism to the new conditions, while other tissues were possibly taking over the functions of the absent organ; and the final period one of comparative equilibrium, approaching the end point of the adjustment process. The immediate increase of all cells after operation suggests the removal of some factor that either restricts production of white cells or destroys those that have passed their usefulness. In the Arneth index we have for the neutrophiles a means of estimating which factor is mainly concerned. In the first period in this case the index was

[8] Jour. de physiol. et de path. gén., 1903, v, 1073.
[9] Med. Record, 1911, lxxix, 110.
[10] Am. Jour. Med. Sc., clviii, 158.
[11] Jour. Am. Med. Assn., 1916, lxvii, 719.

very slightly increased. As the neutrophiles were present in more than double normal numbers it seems probable that the increase was not entirely due to lessened destruction. Moreover, the coincidence of a rise of the index with the first sharp drop of the neutrophiles at the beginning of the second period, the fact that during this period high points in the neutrophile curve tend to coincide with high points of the index, and that the index remained high with a normal number of neutrophiles in the final period, all suggest that the variations in the cell count are due at least in part to variations in the number of cells produced rather than to changes in the rate of destruction. This point of view would result in the conception of the normal spleen as exercising a restrictive action on the production of leukocytes.

SUMMARY. The results of these observations may be summarized as follows:

1. The removal of the spleen resulted in a considerable increase in the total leukocyte count which persisted with much irregularity for over three months.

2. In the early period all types of white cell were increased in nearly the same proportion, although a slight increase of endothelial cells was noted at the expense of the lymphocytes.

3. In the intermediate period both total and differential count showed such marked variation as to render averages valueless, but the total count usually was high.

4. In the final period a comparative equilibrium was reached, with a moderate increase in the total count, due entirely to lymphocytes and endothelial cells while the granular leukocytes showed strictly normal figures.

5. The endothelial cells were constantly increased both relatively and absolutely.

6. The observations on the Arneth index suggest that the increase in the count is at least in part due to the removal of some factor restricting the production of white cells.

7. No eosinophilia appeared during the course of the work.

MODERN INDIVIDUALIZED DIETARY TREATMENT IN DIABETES.

BY MARIUS LAURITZEN, M.D.,
UNIVERSITY OF COPENHAGEN, DENMARK.

Historical Retrospect. The basis of our dietary treatment of diabetes was created at the close of the eighteenth century by the English physician Rollo. The diet then was an animal mixed diet: 1.5 liters of milk, meat, fat and a little bread.

In the fourth decennium of the nineteenth century diabetic therapy began to show signs of individualizing. Bouchardat led the way, calling attention to the fact that milk in addition to animal diet poor in carbohydrates often disagrees with patients and that large rations of meat disagree with certain patients. In cases in which a little ordinary bread leads to glycosuria he used gluten bread or gave vegetables poor in carbohydrates and fruits.

In the seventies the absolute dietary forms flourished for a time. These were Cantani's absolute meat diet and the Englishman Donkin's absolute milk diet. Both writers thought they had found a therapy able to produce a lasting cure of the disease, provided only that the course of treatment were continued for long periods, the meat diet was to be kept from two to nine months and the milk diet no less than six weeks. Not until then might a cautious transition to a mixed form of diet be made. In the same period E. Külz made his researches into the influence of the different carbohydrates on glycosuria.

In the eighties an opposition arose to the strict meat diet as recommended especially by Cantani and Naunyn. It came from Ebstein, who had seen symptoms of threatening coma in a diabetic who had been put on a strict meat diet and in whose urine diacetic acid was shown to be present. Ebstein here originated a most essential individualization in the therapy of diabetes: in the cases in which the urine gives Gerhardt's reaction for diacetic acid a *sudden* exclusion of the carbohydrates of the food, which may greatly endanger the patient, should be avoided.

The use of the diet poor in carbohydrates in diabetes with acetone and diacetic acid in the urine was not, however, abandoned, even though there was a tendency, for some years, to abandon this form of diet in cases of moderate severity; for if only sudden elimination of carbohydrates was avoided, or, on Naunyn's advice, the urine was made alkaline by administering alkali (10 to 30 gm.) before starting strict diet, the threatening coma symptoms were avoided. If then a prolonged strict diet had spared the patient's weakened function, first the diaceturia and then the acetonuria were often seen to disappear.

Clinical experience showed, however, that there were severe cases in which the strict diet poor in carbohydrates did not bring about the disappearance of glycosuria. Already Cantani had in such cases used *short fasting:* keeping the patient fasting for twenty-four hours or longer, he left him without food and with only water or broth a few times a day from one day's evening to the forenoon of the third day. After disappearance of glycosuria Cantani returned to absolute meat diet, giving, however, only one-half or two-thirds of the ration formerly used, and not until fifteen to twenty days later was the meat ration increased. If sugar, appeared, absolute fasting was reintroduced. Naunyn, too, used the fast day,

and Weintraud, his then collaborator, found by means of metabolic experiments that the diabetic after the fast day saved up considerable quantities of N.

In the nineties altogether a more *systematic quantitative individualization* of the diabetic diet set in. Weintraud at the Strassburg clinic and myself in Denmark at Frederiks Hospital experimented with methodic restriction of the content of protein of the diet, increasing at the same time the quantity of fat in cases of moderate severity. By means of metabolic tests Weintraud showed that a patient suffering from severe diabetes who had been rendered aglycosuric kept his body protein and weight when consuming a food corresponding to that of healthy individuals.[1]

In 1898 von Noorden replaced the fast day by the so-called *vegetable day*,[2] on which the patient got nothing but greens, butter, some fat pork, claret and one or two liqueur glasses of French brandy. The vegetable day has essentially the same action on glycosuria and ketonuria as the fast day; in my experience, however, often only if pork be excluded. Five years later von Noorden published the "oat-cure," which he, from 1907, greatly modified, giving, after a few days of strict diet, 1 or 2 vegetable days, then 2 or 3 oatmeal days and then again 1 or 2 vegetable days. If no aglycosuria was attained the whole rotation was repeated once or twice.

The oatmeal treatment proved particularly indicated in cases of moderate severity and severe cases with acidosis. In threatening coma oatmeal soup without butter was used *or* first 1 or 2 fast days (coffee, tea, mineral waters and 100 to 250 c.c. of French brandy or whisky), and when the greatest danger had passed, oatmeal gruel was prescribed.

L. Blum, of Strassburg, replaced oatmeal by *wheat flour*, with mainly the same result. Most practitioners, however, prefer oatmeal. But what was more important was that Blum taught us how to individualize with the quantities of oatmeal, advising in severe cases to use no more than from 150 down to 75 *grams*, by which means aglycosuria was more quickly attained.

Vegetable diet poor in carbohydrates, originally advocated by Kolisch and later by K. Petrén and myself, I now apply frequently in severe cases of diabetes with acidosis, as with this form of diet it is easier to administer small quantities of protein and a little more carbohydrate than it is possible to give in an animal mixed diet. Further, the alkaline reaction of this diet operates favorably in the presence of acidosis, and finally by this diet one is able to *reduce the total metabolism to the lowest point possible* and still satisfy the appetite of the patient and keep his weight. In fact, a low metabolism is

[1] Healthy people use: at rest, 30 to 35 calories; easy work, 35 to 40 calories; medium hard work, 40 to 50 calories.

[2] Or "green-day."

in certain severe cases, a life-and-death question. Only a consistently maintained *minimum diet* will succeed in keeping the percentage of blood sugar low (0.07 to 0.08 per cent.) and the urine free from sugar.

In my lecture given to the Medical Society of Copenhagen in 1912,[3] in which I demonstrated the favorable effect of a *vegetable diet poor in carbohydrates* ("mixed vegetable diet:" greens, eggs, pork, butter, tea, coffee, mineral waters, claret) in the case of diabetic acidosis, I also strongly pointed out that overfeeding the patients in diabetes was hurtful to them, and that a diet that just suffices to cover their requirement is what suits them best. The lives of patients are preserved the longest time in this way.[4]

In 1913 I discussed this question with Weintraud, who two or three times had pronounced in favor of "chronic undernutrition" in case of a severe diabetes.

Experiments with Strict Vegetable Diet. After this retrospect I pass on to the new experiments I have been making during recent years in my clinic.

First a number of experiments with a *strict vegetable diet* applied to both recent and older cases of diabetes. After the disappearance of glycosuria, hyperglycemia and acidosis, if any, a *slow* transition to a mixed diet poor in carbohydrate was made.

After twenty-four to forty-eight hours' observation on mixed food or on the diet prescribed by the practitioner sending him, the patient, in bed, was put on a strict vegetable diet, *i. e.*, 300 to 500 gm. of green vegetables (with 2 to 5 per cent. of carbohydrates), 60 to 75 gm. of butter, 200 gm. of bouillon, 150 gm. of cranberries, 1 egg, tea, coffee, soda-water and, sometimes, alcohol, such as claret, whisky or French brandy.

Vegetable diet was used from two to eight days until aglycosuria was attained and hyperglycemia had disappeared. (See tables I and II.)

In rather mild and fresh cases, glycosuria and hyperglycemia[5] disappeared on the first or second day, in cases of moderate severity and older cases from seven to eight days (see Table I) or even more may pass. If a mild *ketonuria* (acetonuria and diaceturia) is present

[3] Marius Lauritzen: Diabetisk Acidose og dens Behandling (Diabetic acidosis and its treatment), Nord Tidsskr. for Terapi, 1912; Die Therapie der Gegenwart, 1912.

[4] Weintraud wrote me on June 26, 1913 saying: "As to 'chronic undernutrition' and the value of it in treating severe cases of diabetes I have already several times stated my opinion. It is here, of course, not a question of a set form but of a test ('einen tastenden Versuch') of making the patients just keep their metabolic balance with the least supply of nutrition possible. The experience that to attain this end a less copious supply of nutrition than many are used to suffices, even in severe diabetes, contradicts the general opinion of many medical men that any diabetic has to eat more than the healthy individual, and I believe that our dietary treatments many a time are wrecked on this misconception that man has to eat such a lot. The great quantity is often nothing but a bad habit."

[5] In spite of high glycosuria pronounced hyperglycemia may often be absent in fresh cases. (Lauritzen.)

it may disappear quickly. In case of rather high degrees of acidosis it will, as a rule, be diminished, but may increase during the first twenty-four hours, especially if the N excretion in the urine is high and the butter ration is too abundant for the patient's acidosis.

TABLE I.—STRICT VEGETABLE DIET. H. N. P., THIRTY YEARS; MALE; DIABETES; ACIDOSIS.

Date.	Food.	Soda, gm.	Urine sugar, gm.	Blood sugar, %	Ammonia, gm.	N, gm.	Weight, kilos.
June 30	Mixed diet	10	123	0.14	2.4	10.6	63.2
July 1	1. Vegetable day[6]	20	30	....	2.5	10.8	
2	2. Vegetable day	20	21	....	1.68		
3	3. Vegetable day	20	22	....	1.2	5.8	
4	4. Vegetable day	20	12				
5	5. Vegetable day	20	traces	....	....	4.3	
6	6. Vegetable day	20	0	....	0.25	4.8	
7	7. Vegetable day[7]	20	0	0.07	0.25	4.0	63.2

TABLE II.—STRICT VEGETABLE DIET. E. K., FIVE YEARS; DIABETES.

Date.	Food.	Urine sugar, %	Urine sugar, gm.	Blood sugar, %	Ammonia, gm.	N, gm.	Weight, kilos.
May 3	Mixed diet	6.0	24	0.06	0.33	4.9	17.5
4	1. Vegetable day[8]	....	0	....	0.20	4.8	
5	2. Vegetable day	....	0	....	0.79	7.6	
6	3. Vegetable day	....	0	0.05	0.97	5.4	17.3
10	Mixed vegetable diet[9]	....	0	0.05	0.45	4.2	17.4
13	Mixed vegetable diet[10]	....	0	....	....	2.89	17.4
16	Mixed vegetable diet[11]	....	0	0.05	0.24	3.6	17.5

N in the urine falls from the prevailing level (13 to 18 gm.) to 5 to 8 gm. In children N in the urine is, as a rule, lower.

The body weight will often, to some extent decrease as much as 1 kilo or more; in other cases the weight remains almost unaltered.

The *transition* from strict vegetable diet to the diet that suits each patient *is made slowly* to avoid glycosuria, hyperglycemia

[6] Vegetables, 500 gm.; butter, 75 gm.; 1 egg; broth, 200 gm.; cranberries, 150 gm.; tea, coffee.

[7] Then patient passed on to "mixed vegetable diet" and at last roast meat, 50 gm. and cheese, 30 gm. were added. Uses no more soda. Remains sugar-free with normal blood sugar and has mild acetonuria. Is able to work.

[8] Vegetables, 300 gm.; butter, 60 gm.; 1 egg; cranberries, 75 gm.; soup, 200 gm.; tea.

[9] Vegetables, 200 gm.; butter, 60 gm.; 2 eggs; cranberries, 75 gm.; soup, 200 gm.; tea; boiled pork, 25 gm.; roast pork, 25 gm.

[10] + Aleuron bread, 50 gm.

[11] + Roast meat, 25 gm. Gets now mixed diet with gluten bread, 50 gm. (20 per cent. of carbohydrate). Is sugar-free, has normal blood sugar and mild acetonuria. Weight, 19 kilos.

and a sudden increase of acidosis if present. The glycemia is examined after each addition to the food. If hyperglycemia sets in a vegetable day is at once intercalated, thus often avoiding the occurrence of glycosuria, which I consider of great importance.

In *mild* cases the first additions to the vegetable diet are proteins: one or two eggs or 50 gm. of roast meat or of fish; next further additions of protein and fat, when the ration of vegetables may simultaneously be restricted to 300 to 400 gm.

In cases of *moderate severity* the first additions are fatty foods: 25 gm. of roast pork at a time, then boiled striped pork, eggs, fish and, at last, meat, always small additions. When acetonuria has disappeared the rations of vegetables are restricted to 300 gm., and fish and roast meat are increased to 150 gm. (to be weighed after preparation).

In *severe* cases, with rather strong acidosis, strict vegetable diet should be continued during several days, up to one week, and if this results in the elimination of glycosuria and in bettering acidosis, the patient gets small additions of roast pork, then of eggs and boiled pork and alcohol. If these additions are tolerated, fish, ham and meat are tried, but no more than 50 gm.

In strict vegetable diet I prescribe *alkalies* (sodium bicarbonate and citrate) as little as possible, these substances together with this diet easily causing retention of water and edema. Only in case the alkaline diet is unable by itself to keep the quantity of ammonia in the urine within normal limits, bicarbonate in doses of 5 gm. and upward, as suited to each case, may be given.

The advantage of *strict vegetable diet* over the gradual restriction of the carbohydrate and protein of the food is that aglycosuria and removal of hyperglycemia are *more quickly* attained, but in order to attain a result no less permanent and good than by gradual restriction the *transition* from vegetable diet to mixed diet poor in carbohydrates should be made quite slowly and according to the above-stated rules.

In the after-treatment *overfeeding should be avoided*, the patient getting the exact food rations that keep up his weight, and in young people and children the weight is to rise slowly, a quick increase of weight often causing glycosuria.

In cases of moderate or great severity large rations of protein should be avoided, especially protein of meat and casein.

I give in *mild* cases of diabetes from 1.5 to 2 gm. of protein per kilo of body weight; in *moderately* severe ones 1.0 to 1.5 gm. of protein per kilo of body weight; in *severe* cases 0.5 to 1.0 gm. protein per kilo of body weight.

It is difficult to fix precise caloric amounts for the food as a whole. It is necessary to individualize, trying by means of frequent weighings to find the right amount.

TABLE III.—P. H., SEVENTEEN YEARS; APPRENTICE; DIABETES OF MODERATE SEVERITY; ACIDOSIS.

Years, dates.	Protein.	Fat.	Carbohydrate.	Urine sugar, %	Urine sugar, gm.	Blood sugar, %	Acetonuria.	Diaceturia.	Weight, kilos.
1911, Sept. 1[12]	...	...	...	8.75					
1911, Sept. 21[13]	...	...	...	5.0	100	.....	+	+	50.4
1911, Oct. 20	98	181	24[14]	....	0	.....	+	÷	51.0
1912, Jan. 3	98	181	24	....	0	.....	+	÷	54.0
1913, Jan. 1	134	220	52[15]	....	0	.....	+	÷	54.0
1913, Oct. 27	134	220	52	....	0	.....	÷	÷	56.0
1914, Mar. 31	123	223	58[16]	....	0	.....	+	÷	
1914, Apr. 18	123	223	58	....	0	0.083	+	÷	54.0
1915, Apr. 10	123	223	58	....	0	0.085	+	÷	56.0
1916, Sept. 6	123	223	58	....	0	.....	÷	÷	56.0

TABLE IV.—OATMEAL TREATMENT AND PROLONGED MIXED VEGETABLE DIET. F. P., THIRTEEN YEARS; BOY; DIABETES OF MODERATE SEVERITY; ACIDOSIS.

Date.	Food.	gm. soda.	% urine sugar.	gm. urine sugar.	% blood sugar.	Diaceturia.	gm. ammonia.	gm. N.	Weight, kilos.
1915, Jan. 18	Mixed diet	..	8.0	80	0.15	+	....	....	28.8
19	1. Vegetable day	..	6.0	60	....	++			
20	2. Vegetable day	..	3.0	23	....	++			
21	1. Oatmeal day[17]	..	1.25	25	....	÷			
22	2. Oatmeal day	..	1.0	22	....	÷			
23	1. Vegetable day	..	0.5	8	....	÷	....	....	28.9
24	2. Vegetable day	..	0.25	4	....	÷			
25	3. Vegetable day	..	....	trace	....	+			
26	Oatmeal day	..	0.25	6	....	÷			
27	1. Vegetable day	..	....	0	....	+	....	3.07	28.4
Feb. 1	Mixed vegetable diet[18]	2½	....	0	....	+	....	....	29.1
1916, Aug. 22	Mixed vegetable diet	2½	....	0	0.07	+	1.29	4.2	35.0

When a diabetic has been freed from glycosuria and acetonuria or has but a weak acetonuria left, the *minimum* will most frequently be 30 calories per kilo and sometimes less. If the patient performs light work from 35 to 40 calories; if heavier work above 40 calories will most frequently be the proper allowance.

In very young persons and children the amount of calories per kilo is *higher*. The following are examples:

[12] Mixed food.

[13] Diet with gluten bread from September 2.

[14] About 2200 calories. Carbohydrates in greens and compotes (light work).

[15] About 2800 calories. Carbohydrates in greens and compotes; gluten bread (heavier work).

[16] About 2800 calories. Carbohydrates in greens and compotes; gluten bread.

[17] Oatmeal, 75 gm.; butter, tea, 60 gm.

[18] Vegetable, 500 gm.; butter, 75 gm.; 2 eggs; pork, 100 gm.; soup, 200 gm.; cranberries, 150 gm. = 36 gm. of protein, 160 gm. of fat, 169 gm. of carbohydrate = 1753.

A male, aged seventeen years, with diabetes of moderate severity, used in his seventeenth and eighteenth years from 43 to 41 calories per kilo at *light work*, in his ninteenth to twenty-second years about 53 calories at *heavy* work. (See Table III.)

A boy, aged thirteen years, used in his thirteenth and fourteenth years 1750 calories or from 58 to 50 calories per kilo. His weight rose from 29 to 35 kilos. (See Table IV.)

Experiments with Prolonged Fasting. In a number of cases I have used prolonged fasting as recommended by Frederick M. Allen.[19]

On the basis of experiments made by him with fasting and then scanty feeding in diabetic dogs after partial pancreatectomy, Allen proposed to try similar prolonged fasting in diabetes in man, using after the fast small food rations that prevented any important increase of weight, glycosuria and, as far as feasible, acetonuria.

Allen's method of treatment is as follows:

1. *Fast days* (patient only gets coffee up to seven times daily, and, contingently, whisky in rather large doses, sometimes some 200 gm. and, in the case of considerable acidosis, sodium bicarbonate). Fasting is to be continued until the disappearance of glycosuria and preferably one or two days longer.

2. The day after fasting from 200 to 300 gm. of greens low in carbohydrates are given, which are increased from day to day, until reappearance of a little sugar in the urine. Then again one fast day.

3. After this *protein* is given. On the first day 1 or 2 eggs, then more protein in the form of eggs and meat, until the urine contains a little sugar. Then another fast day.

4. At last fats are given in gradually increasing quantities.

With patients that cannot be kept aglycosuric on low-class vegetables (with 4 or 5 per cent. of carbohydrate) these vegetables are boiled a few times and the water is strained off.

In patients made aglycosuric, Allen now and then saw mild glycosuria appearing after somewhat plentiful addition of fat, and in such cases he takes care not to give large fat rations.

At the Hospital of the Rockefeller Institute, Allen tried the treatment of prolonged fasting in 100 cases, and he thinks that aglycosuria was attained more quickly than by means of gradual restriction of carbohydrates and protein. Allen urges that after fast days the supply of food should not increase too quickly and that the patient's loss of weight during fasting should not cause alarm. Altogether, Allen is of opinion that a reduction of weight is in itself beneficial to the diabetic and serves to spare the weakened function and increase tolerance.

The treatment with prolonged fasting was tried in 8 cases by L. M.

[19] Allen, F. M.: The treatment of diabetes, Boston Med. and Surg. Jour., February, 1915. Prolonged Fasting in Diabetes, Am. Jour. Med. Sc., October, 1915. Allen, Stillman and Fitz: Rockefeller Institute Monograph, No. 11, 1919.

Hill and I. L. Sherrick[20] (Boston). They praise the method, proceeding, however, in a somewhat different way: After fast days until aglycosuria was attained they gave one vegetable day with 15 gm. of carbohydrate and then one day a diet containing 15 gm. of carbohydrate, 25 gm. of protein and 150 gm. of fat. After this they gradually increased fat, then protein and, at last, carbohydrate. Of fat they did not give more than 200 gm., and the amount of calories rarely exceeded 2200 per day.

Elliot P. Joslin,[21] too, has used Allen's prolonged fasting treatment following his indications. After fasting, however, he gives only 150 gm. of vegetables, then fruit poor in carbohydrate, then protein, and finally fat until the patient ceases losing weight.

In the cases in which I have tried prolonged fasting it was not always as easy to carry through the treatment as with the strict vegetable diet, some few patients objecting, others being psychically affected in a less fortunate way by the fast which, surely, has the drawback of being rather severe.

The following are a few instances of the fasting treatment (Tables V and VI):

Table V.—Female, aged thirty-five years, suffering from adipositas, *mild* diabetes and gangrene in crus. She had had diabetes for several years, and shortly before entering the clinic she had 7 per cent. of sugar; no albuminuria or acetonuria. On entering she had a gangrenous ulcer the size of a palm on left crus. After the third fast day the urine was sugar free and hyperglycemia had disappeared. *Now acetonuria and diaceturia appeared*, remaining during the following vegetable days without entirely disappearing, until mixed diet with 20 gm. of gluten bread and 300 gm. of greens was begun. On this diet she remained free from glycosuria and hyperglycemia. The *gangrenous ulcer* healed entirely. Patient is constantly sugar free. She now gets 100 gm. of gluten bread (with 20 per cent. of carbohydrate) per day.

Table VI.—Female, aged thirty years, with *severe* diabetes and acidosis. Patient had been suffering from diabetes a year, and had for several months been free from glycosuria and hyperglycemia, with mild acetonuria. Some weeks before entering the clinic glycosuria and hyperglycemia had set in again owing to a faulty diet. On the second fast day the urine became sugar free and remained so (except on September 26) during slow transition to mixed vegetable diet, which she still keeps. The table shows how the percentage of blood sugar becomes normal.

During fasting acetonuria and diaceturia behave differently (see tables), according to whether the cases of diabetes under treatment are mild or severe. In *mild* diabetes acetonuria and diaceturia

[20] Boston Med. and Surg. Jour., 1915, p. 696.
[21] Am. Jour. Med. Sc., 1915, p. 485.

appear on the second or third fast days, continuing on the following vegetable days, but disappearing on transition to mixed diet with more carbohydrate. In *severe* diabetes with acidosis the latter *decreases, i. e.*, acetonuria and diaceturia abate and the quantity of ammonia in the urine diminishes. On the following vegetable days the quantity of ammonia increases again, owing to a sudden supply of nourishment (fat and protein). It is a well-known fact that in the case of severe diabetes metabolism of fat from the food increases acidosis more than metabolism of fat from the organs. After a few days of vegetable diet the quantity of ammonia again becomes normal.

TABLE V.—FASTING TREATMENT. A. H., FIFTY-FIVE YEARS; FEMALE; MILD DIABETES; GANGRENE.

Date.	Food.	Sugar, %	Sugar, gm.	Blood sugar, %	Diaceturia.	Ammonia, gm.	N, gm.
July 4	Mixed diet	7.0	70	....	÷		
Aug. 5	Diet with 100 gm. gluten bread	1.0	12	0.17	÷		
9	1. Fast day	...	traces	....	÷	....	6.24
10	2. Fast day	...	traces	....	÷	0.52	6.94
11	3. Fast day	...	0	0.07	++	0.75	5.92
12	Vegetable day	...	0	....	++	1.6	9.09
13	Vegetable day	...	0	....	++	1.2	5.96
14	Mixed diet[22]	...	0	....	+	1.12	5.49
16	Mixed diet[23]	...	0	0.08	÷	0.7	

TABLE VI.—FASTING TREATMENT. A. P., THIRTY YEARS; FEMALE; SEVERE DIABETES; ACIDOSIS.

Date.	Food.	Sugar, gm.	Blood sugar, %	Ammonia, gm.	N, gm.	Weight, kilos.
Sept. 22	Diet with 30 gm. gluten bread	21	0.155	1.61	8.69	50.2
23	1. Fast day	13	....	0.43	5.90	49.2
24	2. Fast day	0	....	0.51	5.72	48.2
25	Vegetable diet[24]	0	....	2.0	6.92	48.6
26	Mixed vegetable diet[25]	traces	0.096	0.99	6.66	48.6
27	Mixed vegetable diet[26]	traces	....	0.93	5.32	48.6
28	Mixed vegetable diet[27]	0	....	1.7	5.33	49.2
29	Mixed vegetable diet[28]	0	0.075	1.05	5.29	49.2
30	Mixed vegetable diet[29]	0	....	0.68	4.86	49.3

[22] Roast meat, 50 gm.; pork, 59 gm.; 1 egg; butter, 60 gm.; vegetables, 300 gm.; cranberries, 150 gm.; one-third bottle of claret, tea, coffee.

[23] + Gluten bread, 30 gm.

[24] Vegetables, 400 gm.; butter, 60 gm.; soup, 200 gm.; cranberries, 150 gm.; tea, coffee, 30 gm.; French brandy.

[25] + 1 egg and roast pork, 25 gm.

[26] + 1 egg and roast pork, 25 gm.

[27] + Boiled pork, 25 gm.

[28] + Roast pork, 25 gm. and butter, 15 gm.

[29] + Roast meat or fish, 50 gm.

The excretion of N in the urine depends, of course, on the supply of protein on the days preceding the fast days.

(In *healthy individuals* the quantity of N in the urine is rarely, in case of fasting, less than 10 gm. On the second day, and often not until the third or fourth days, N in the urine *rises*, an occurrence which probably is due to the fact that the stock of glycogen of the body diminishes and, on the third day, is exhausted. After this rise the metabolism of protein *decreases* slowly during continued hunger. During the first ten days it rarely sinks under 10 gm.).

The same state of things as in healthy persons I found in diabetics on fast-days. That the N figures in these two cases were lower was due, no doubt, to the patients being beforehand on a food poor in protein. On the first vegetable day after fasting N rises in the urine, but it soon decreases again on mixed vegetable diet. (I met with the same state of things in my experiments with *strict vegetable diet*. See Tables I and II.)

The Modern Individualized Diabetic Diet in Practice. It follows from what is stated above that diabetic therapy has been developing more and more toward individualizing dietary treatment.

This was bound to be the case, the closer study of diabetes showing doctors the diversity of the disease: first the mild functional troubles that remain mild for years without dietary treatment of any importance, then other mild cases that owing to complication with other diseases demand a thorough change of the ordinary diet, and then other mild cases that, now suddenly now gradually reveal themselves as severe diabetes. Finally there are the cases of moderate severity with ketonuria, which may be expected soon to grow severe; they are changed by strict treatment into mild ones, the urine remaining normal for years.

It is evident that a single dietary scheme does not suit these different forms and stages of the disease. Each patient has to be carefully examined and be treated with the diet that qualitatively and quantitatively suits him at the time. Not only the content of carbohydrate of the diet, but also the rations of protein and fat should be empirically fixed according to the stage of the disease.

Some old and modern methods of treatment, such as absolute milk diet, oatmeal treatment, the strict vegetable treatment and fasting, proved of importance as passing short treatments in certain fixed cases and under dangerous situations, and they are of great use to us when applied with good judgment and prudence.

The forms of diets used during long periods, such as "animal diet poor in carbohydrate" and "mixed vegetable diet," are tolerated by many patients for years. If dyspepsia, which may be preliminary to threatening coma, appears, the great point is to break off in time, giving various small rations of carbohydrates or prescribing fasting or oatmeal gruel diets. After disappearance of dyspepsia the diet poor in carbohydrate may be prudently resumed, when a period

again sets in during which the patient may for months or years be kept free from glycosuria and acetonuria or with a slight acetonuria. At last in *severe* diabetes a time will come when the effort of keeping the patient aglycosuric by means of the above strict forms of diet will fail, and at the same time as glycosuria increases acidosis will gain strength. Then, before all, it should be tried to better the patient's function by one of the above-mentioned methods of treatment: strict vegetable treatment, oatmeal treatment or prolonged fasting. If these attempts fail, there is nothing left but prescribing a mixed diet somewhat richer in carbohydrate. This will increase the patient's glycosuria sometimes slowly, in other cases more quickly. In the former case acidosis will remain moderate, but if glycosuria increases quickly, acidosis will gain strength too, sometimes in a higher degree than glycosuria.

I shall now describe the *dietary treatment* of diabetes as carried on at present in my clinic, of course in its broad features only.

Complication with other diseases may, as a matter of course, influence the dietary treatment. So such cases will be mentioned by themselves.

Fresh Uncomplicated Cases of Diabetes manifest themselves as *mild* cases or as *cases of moderate severity.* (It is very rare to observe a fresh case that from the very beginning is severe. It is nearly always possible through anamnesis to show that the disease has been in existence a short or long time previously without being discovered.)

In the presence of an apparently *mild diabetes* I give the patient for a day or two mixed food or the diet prescribed by the practitioner who sent him to the clinic. At the same time blood sugar, urinary sugar, N and ammonia in the urine of the last twenty-four hours, which is also tested for acetone, diacetic acid, albumin, etc., are quantitatively determined. Then diets are prescribed as follows:

1. *Test diet* for two or three days. The test consists of 150 gm. of roast meat, 4 eggs, 80 gm. of butter, 50 gm. of cheese, 300 gm. of vegetables (with 2 to 5 per cent. of carbohydrate), 100 gm. of compote of rhubarb, 200 gm. of broth, 100 gm. of cream, 100 gm. of bread, one-third bottle of claret, 500 gm. of tea, 500 gm. of coffee, 500 gm. of soda water. This diet contains 104 gm. of protein, 140 gm. of fat, 72 gm. of carbohydrate, 18 gm. of alcohol = 2151 calories. In some mild cases the urine will be sugar-free in two or three days. If this is not the case, or if the percentage of blood sugar remains above the normal on such food, that is, 0.08 to 0.09 per cent., then

2. *Vegetable diet* (see above) is prescribed for one day, when

3. *Animal diet* as in the test diet is prescribed, but without cream, bread being, according to the nature of the case, replaced by 60 to 120 gm. of gluten bread or left out altogether, or changed for vegetables very poor in carbohydrates. The rations of gluten bread or vegetables which are tolerated without developing hyperglycemia after the meal are prescribed.

The diet fixed in this way is kept *for months*, often *for a couple of years*, before further additional carbohydrates are admitted, and is constantly controlled by blood analyses. *Milk* is never prescribed in uncomplicated cases, nor *cream* either, only exceptionally 50 to 100 gm. of "whipping" cream.[30] Now and then it occurs that the patient, after a couple of years, is able to pass on to ordinary mixed diet (with no sugar in it) without developing glycosuria.

In mild cases, too, which, when following their normal course, pass off without any lasting acetonuria and diaceturia, the diet poor in carbohydrate may be seen to develop ketonuria at the beginning of the treatment. The ketonuria, however, disappears little by little as carbohydrate tolerance improves, and may often be got rid of by increasing the protein of the food, protein in this case acting on acetonuria in the same way as addition of carbohydrate (as in healthy individuals) in contrast with what is seen in severe cases when additional protein is apt to increase acidosis.

In *uncomplicated cases of apparently moderate severity* or when a case that to begin with was considered a mild one proves to be of moderate severity, that is one in which the above test-diet less bread, cream, cheese, wine and butter (kneaded in water) to which vegetables very poor in carbohydrates are added, is unable to remove hyperglycemia and glycosuria, various methods may be made use of:

1. The treatment described above, with *strict vegetable diet* for several days, may be applied until the attainment of the desired result, when a *slow* passage to mixed diet poorer in proteins than the first diet is made.

2. Instead of strict vegetable diet *fasting* may be used as advised by Cantani or Allen, followed by a *slow* passage to a diet poor in protein.

3. One may rest content with intercalating *one vegetable day at a time* and then pass to a diet poorer in protein intercalating, if needed, another vegetable day, after which the ration of protein is further restricted, until blood sugar and urine are normal. If the case is one apt to develop ketonuria, as in children and very young people, I generally have recourse to

4. Von Noorden's "oat cure" with the rations of oatmeal and butter (kneaded in water to remove fatty acids) that are suited to each individual case; after the concluding vegetable days I *slowly* pass to strict animal diet with vegetables.

(N. B.—If the patient is not in hospital or clinic, and if one does not fully master the technic of vegetable treatment, fasting treatment or "oat cure," method No. 3 should be chosen as being *harmless*, easily carried through and productive of results that are equal to what is attained by means of the other methods, as long as it is a diabetes of moderate severity).

[30] First-class cream used for whipped cream.

If the presence of diaceturia should in any way trouble the practitioner then, besides the vegetable days intercalated, which effect a lowering of acidosis, small doses of *alkalies* may be used, increasing from 5 gm. per day until the urine is alkaline.[31]

Diabetes of moderate severity which is not treated or not treated with sufficient energy and length of time with small food rations preventing hyperglycemia and glycosuria will more or less quickly pass into the last stages of the disease. We shall then be face to face with the *severe* and *severest* cases in which *diabetic acidosis* has such great influence on the treatment.

In *severe cases* of diabetes with *acidosis of moderate severity* in which the quantity per day of ammonia in the urine is from 2 to 3 gm. (on mixed antidiabetic diet with some 30 gm. of carbohydrate) it should always be tried by means of energetic treatment to change the case from a severe one into a moderate one, a plan which will often prove a success.

In my clinic we observe the patient a couple of days on the diet he follows at the time, determining daily ammonia, urinary sugar and N in the urine. The pulse is daily examined in view of acidosis. Analysis of blood sugar is made at least twice a week. If the patient uses soda he continues the same dose. He is out of bed resting two or three hours daily.

As a rule, *treatment* (3) (see above) is now applied with reduction of the protein of the food, especially meat and food containing casein (cream, cheese, milk).[32] Thus both protein and carbohydrate are gradually restricted, being replaced by green vegetables until the attainment of aglycosuria and the lowest percentage of blood sugar possible, best of all 0.05 or 0.06 per cent. If for some reason or other, *quick* attainment of sugar-freedom is wanted, *vegetable treatment* (1) or *fasting* (2) with confinement to bed are used, being continued until the object is attained. In case aglycosuria and hypoglycemia are not attained by treatment (3), acidosis being heavier than usual, I try von Noorden's *oatmeal treatment.*

If one of the above treatments proves successful in rendering urine and blood normal and removing ketonuria, *diet poor in protein + vegetables poor in carbohydrates with washed-out butter* or with olive oil, vinegar and other spices, and for drinks, soda water, tea, coffee, aquavitæ or French brandy, should be continued as long as possible. The patient's life may then be preserved for years. If dyspepsia sets in the treatment is broken off, the diet being modified or one or two days' fasting prescribed.

In *the severest cases with heavy acidosis*, when there are 4 to 8 gm. of ammonia in twenty-four hours (on mixed diet with about 30 gm.

[31] The first days of alkali therapy may cause an increase of acetonuria and diaceturia, but the addition of alkali should be continued, until the urine is alkaline.

[32] My experience is that in these cases, too, these proteins are less well tolerated than vegetable protein.

of carbohydrate) the treatment is attended with greater difficulties. Here we, as a rule, also have *obstipation* and *dyspepsia* to contend with.

Confinement to bed for a more or less extended period is necessary. The degree of acidosis will somewhat diminish through *vegetable treatment* or *fasting* with or without subsequent *oatmeal treatment.* Also *alkalies* should be used to obtain alkaline urine. Though glycosuria may not be quite removed, it may often be lowered to from 10 to 20 gm. in twenty-four hours, and ammonia to 0.5 or 1 gm.

The diet of the *after-treatment* must contain *very small quantities of proteins,* especially vegetable protein and protein of hen's eggs, which are better tolerated here than any other. The carbohydrate of the food must be derived from vegetables and fruits containing little carbohydrate; if required, small rations of bread are given. Milk and cream had better be avoided, both milk sugar and casein affecting glycosuria unfavorably, but should at times be conceded to give a variety to food. Of *fats,* vegetable fat, butter (kneaded in water) and pork are given, but all in rather small rations on account of acidosis, which at this stage is rather sensitive to fats. *Alcohol,* on the contrary, acts favorably, being almost indispensable and full of advantages. Patients tolerate large doses of it; it does not increase glycosuria and has a good effect on acidosis. Good claret, hock, sugar-free champagne, French brandy, whisky, aqua vitæ are given according to the patient's liking.

If small helpings (25 to 50 gm.) of roast meat or fish agree without a great increase of glycosuria or acidosis, they give a good variety to diet.

Coma Diabeticum Incipiens. In acute exacerbation of acidosis, which is preliminary to coma, we see the precomatose symptoms: increased thirst, troubled sleep, headache, rapid pulse and respiration with deep inspirations. An energetic and consistent treatment at this first stage of coma nearly always takes the patient over the serious situation; but at the somnolent stage, too, one often succeeds in bringing about a lasting cure. On the contrary, in the case of deep coma I have never obtained more than a brief restoration to consciousness by means of *intravenous injections* of a 3 per cent. solution of sodium bicarbonate (solution sterilized in a not hermetically closed flask over the fire for ten minutes). From 25 to 30 gm. sodium bicarbonate are injected.

In the *first stage* of coma incipiens: confinement to bed, absolute quiet, surveillance by a trained nurse and the doctor the few hours during which there is any hope of saving patient. The latter is kept warm. Every quarter of an hour he gets a teaspoonful of sodium bicarbonate well stirred in water; camphorated oil frequently injected subcutaneously and, in case of specially weak action of the heart, digalen (1 c.c. intravenously) or strophanthin, Boehringer ($\frac{1}{2}$ to 1 mg. intravenously). If no *quick* improvement sets in, with

the pulse becoming less rapid and respiration normal, the treatment with soda every quarter of an hour and heart tonics is continued. As soon as the state has improved the intestine is evacuated without making any tax upon patient (decoction of senna and enema of 3 parts of water + 1 part of glycerine, if any). Directly after defecation camphorated oil is administered subcutaneously.

Diet. Formerly absolute milk diet was used and, after the introduction of the "oat cure," only oatmeal gruel made of 100 to 150 gm. of oatmeal without butter, hot or cold with lemon, especially with emaciated patients that are thought not to have taken any excess of nourishment immediately before coma. But otherwise, for twenty-four to forty-eight hours, I use no food but alcohol (French brandy, whisky) diluted with water, and then oatmeal gruel diet for one or two days. If then the patient has an appetite, further 150 gm. of vegetables with 20 gm. of butter are given and, for dinner, broth with vegetables. The passage to mixed vegetable diet with restriction of the oatmeal ration is slow, and the dosage of soda required to keep the twenty-four-hour urine alkaline is provided. Confinement to bed continues at least four weeks after incipient coma is well over.

Diabetic Therapy in Children. 1. In infants in the first or second years of life the course is rapid, and in no case did I succeed in improving function to any essential degree. After water diet I passed to milk mixture *or* oatmeal gruel, or mixed vegetable diet.

2. In older children in whom *glycosuria* is found I give, after a strict vegetable diet, an animal diet poor in carbohydrates and then with caution gluten bread or aleuron bread to the extent tolerated without developing hyperglycemia and glycosuria.

A child, aged five years, weight 18 kilos, received 2 eggs, 60 gm. of pork, 60 gm. of butter, 25 gm. of roast meat or fish, 150 gm. of green vegetables, 45 gm. of gluten bread and 75 gm. of cranberries. The urine remained sugar-free; blood sugar 0.06 per cent.; slight acetonuria and N 4 to 5 gm. in twenty-four hours. The child has one vegetable day and then one day without bread per week.

Diet must be continued for two years before more carbohydrates are allowed and only with control of blood sugar.

In cases of mild glycosuria cure was sometimes obtained through prolonged strict diet. In cases of *moderate severity* and in *severe* cases an energetic treatment may greatly better prognosis *quoad durationem vitæ*, but sooner or later coma will occur. Here I use confinement to bed and after removal of hyperglycemia and glycosuria by means of one of the 4 above stated treatments I pass to mixed vegetable diet continuing keeping it as long as there is a possibility of carrying it through.

Example: Boy, aged thirteen years, suffering from diabetes mellitus and acidosis. Admitted on January 18, 1915. Diabetes began

December, 1914. There was 8 per cent. of sugar in 1000 c.c. of urine; acetonuria and diaceturia. After vegetable treatment combined with oatmeal treatment urine and blood were rendered normal. Slight acetonuria continued.

In 1915 the patient was on 100 gm. of pork, 2 eggs, 200 gm. of broth, 500 gm. of vegetables, 75 gm. of butter and 150 gm. of cranberries and rhubarb = 36 gm. of protein, 160 gm. of fat, 28 gm. of carbohydrates = 1753 calories. Body weight oscillating between 29 and 34 kilos.

In 1916–1919 same diet as in 1915. Urine: sugar, 0; blood sugar, 0.07; slight diaceturia, about 1 gm. of ammonia, N, 3 to 4 gm. Body weight, 35 kilos.

The boy is quite well and able-bodied at his home, a small place in the country.

Children that are more spoiled will, as a rule, require a greater variety of diet.

Diabetes Complicated with other Diseases. It would take us too far afield to speak of the treatments used in all the complicated organic diseases met with in diabetes, but some of the most important must here be included.

Diabetes with Diseases of the Kidneys. In the case of *albuminuria* appearing and disappearing without other signs of chronic nephritis, care should be taken not to give too large rations of meat and eggs and to avoid concentrated spirits and sharp spices.

Chronic nephritis in diabetes calls for greater changes of diet. If in a diabetic *acute exacerbation* occurs in nephritis, for instance on a diet too rich in protein,[33] I use, in my clinic, *absolute milk diet* (1500 c.c. of milk or partly buttermilk, 250 c.c. of water or no water). Then glycosuria will often disappear, the retention of sodium chloride be removed and edemas, if any, disappear. General health improves. Then passage to mixed diet with gradual restriction of milk and addition of vegetables, fruit, butter, some roast meat or fish. At last the diet will be, for instance: 50 gm. of roast meat or fish, 1 egg, 100 gm. of unsalted butter, 200 gm. of vegetables, 50 gm. of unsalted bread, 500 gm. of milk, 250 gm. of cream, and 200 gm. of fruit (= 50 gm. of protein, 160 gm. of fat, 80 gm. of carbohydrate = 2066 calories).

In certain cases of moderate severity doing away with milk and cream altogether will be attempted, giving more vegetables and compote and 125 gm. of "whipping" cream thinned with water. Daily quantity of liquid 1500 to 2000 c.c. Of spices: vinegar, lemon, some vanilla. Of alcoholic drinks: 1 glass of mild claret or Moselle with water.

Diabetes with Diseases of the Vascular System and Heart. Arteriosclerosis is widespread among fat and elderly diabetics. It is met

[33] Or in the case of acute infection.

with only rarely in young individuals suffering from severe diabetes. There is good reason to use moderate rations of eggs and meat, prescribing plenty of vegetables, also bread and, if need be, milk, no more, however, than will keep down glycosuria.

Attacks of cardiac asthma or angina pectoris or tendency to asystole indicate[34] absolute milk diet, as stated above, for a short time (and then passage to mixed diet). Absolute milk diet, in connection with confinement to bed, is of use, too, in the case of *valvular defects* with failing compensation. Also when *circulatory disturbances in the liver* or *chronic hepatitis* exist, milk diet may periodically be used with advantage.

In diabetes with chronic disease of the pancreas in which intestinal utilization of protein and fat is defective treatment with *pancreon*, 5 or 6 gm. daily, which is a great aid to absorption, is used for years with intervals of a few weeks. In mild cases *diet* is as usual. In cases of moderate severity it is not always easy to find the proper diet. By way of example: a man, aged forty-eight years, received, after removal of glycosuria and acetonuria, 150 gm. of roast meat, 50 gm. of pork, 4 eggs, 50 gm. of cheese, 100 gm. of butter, 300 to 400 gm. of vegetables, 100 gm. of cranberries and rhubarb; ½ bottle of claret and two small glasses of aqua vitæ. He used 5 or 6 gm. of pancreon per day with intervals of a few weeks.

Diabetes and Tuberculosis of the Lungs. According to my experiences the patient should go through a regular antidiabetic treatment in hospital so as to remove glycosuria and hyperglycemia. If this result is successfully maintained for months, it acts favorably on tuberculosis of the lungs. After this the patient may, if desired, be sent to a sanatorium for tuberculosis of the lungs, adhering to the diet required. In case of severe acidosis and prognosis pessima, the patient as far as possible should stay at his home.

Diabetes and Acute Febrile Diseases. In severe infections diet is to consist of liquid food, whereas in milder diseases one may, as a rule, be content with modifying the diet used at the time.

In *acute pneumonia* in a *mild* diabetes the prescription of the first days is: 1 liter of cooled milk and ½ liter of lemon-juice in water with saccharine, 1 cup of broth. If at night the thirst is very intense, then three or four times 100 c.c. of lemon-juice with water. The following days, until the crisis comes, care is taken to increase gradually the quantity of food: 1½ liters of milk and ½ liter of cream, the latter to be thinned with water and kept in a cool place. The heart is stimulated by 60 c.c. of fine French brandy and ¼ liter of dry sherry. After the crisis the same food is given a few days, when the mixed diet formerly used is gradually resumed.

[34] In these cases I also obtained a capital effect by using fasting for some days and then reduced vegetable diet.

In cases of *moderate severity* with acidosis I use oatmeal gruel diet suited to each special case, and alcohol in large doses. When there is no more fever one vegetable day is intercalated, and, by a frequent use of vegetable days, reintroduction of the diet poor in carbohydrate is attempted.

In *influenza* with a high fever and *typhoid fever* diet is essentially as stated above, only in the latter case solid food is not to be given until at least a week after the fever has entirely ceased.

In *diabetes* complicated with *adipositas* and *gout* due regard should, of course, be had, in diet, to these diseases. The same thing holds good of diabetics suffering from *diseases of the stomach and intestine, diseases of the skin, morbus Basedowii* and *nervous diseases.* Thus, whereas fasting may be suitable in diseases of the stomach and intestine, it cannot be used in Basedow's disease or with highly nervous diabetics.

As to *syphilitic* diabetics I always submit them to an antiluetic treatment at the same time as diabetic treatment is carried through.

In *diabetic gangrene* it is of great importance to remove hyperglycemia as quickly as possible. Here I use *strict vegetable* diet or *fasting* according to the state of the patient. Blood sugar is frequently examined.

Before *operating* on diabetics glycosuria and hyperglycemia should, as far as possible, be removed. In case of acidosis the urine must be made alkaline by vegetable diet, if need be by alkalies, and should be kept slightly alkaline for some time after operation until all danger of threatening coma seems passed.

Finally a few words on *prophylaxis in diabetes.*

1. In families in whom diabetes occurs the doctor should now and then test the children for glycosuria, particularly after acute febrile diseases, in furunculosis or in case of other symptoms indicative of hyperglycemia, eventually prescribing a starchy meal and examining the urine passed after the lapse of four hours. In diabetic families it stands to reason that the doctor directs parents as to the children's mode of life so as to avoid a food too rich in carbohydrates.

2. In life-insurance examinations, in polyclinics and hospitals, when a reduction is found in the urine of a patient, an examination after a test-meal should be made in doubtful cases. Diabetes may thus often be discovered in its incipient stage.

ROENTGEN-RAY STUDIES OF BRONCHIAL FUNCTION.[1]

By Jesse G. M. Bullowa, M.D.,
AND
Charles Gottlieb, M.D.,
NEW YORK.

(From the Department of Physical Diagnosis, Fordham University.)

Several clinical problems, among them the accumulation of abundant bronchial secretion in laryngeal diphtheria and the formation of bronchiectases and antra, seem to depend upon a more correct understanding of the processes by which the lungs evacuate themselves.

Fluoroscopic observations and studies of the radiographs of an injected tracheobronchial tree in a patient suffering from a malignant tracheo-esophageal fistula seemed to disclose what we interpreted as the evidence of a peristaltic action in the bronchi. Another case, Beeler's,[2] has been reported, but the reduced reproduction of the bronchi does not lend itself to interpretation of detail. Both our own case and that of Beeler died as the result of lung suppuration.

This is not remarkable in view of the fact that infected fluids were injected and in both cases, it is believed that the fistula interfered with the proper emptying of the lung.

Rosenberg, in 1887, was the first to inject the bronchi therapeutically. Chevalier Jackson reported the insufflation of bismuth powder and recommended its utilization in diagnosis. The experiments of C. A. Waters, S. Bayne-Jones[3] and L. G. Rowntree were performed to study the anatomy of the bronchial tree and record the use of thorium and iodoform and bismuth pastes. Some of the dogs in which iodoform was used died.

Our first experiment was with a fox terrior bitch, 20 c.c. of thorium nitrate in sodium citrate solution being injected into the bronchial tree through a catheter. In spite of the prompt evacuation of the thorium solution, by posture, the animal experienced marked dyspnea, rapid irregular heart action and died about fifteen minutes later. A slide of this lung showed that the thorium had already penetrated the pulmonary vessels by osmosis. In another dog, which died from chloroform anesthesia, the excised lungs were filled with thorium solution and radiographed. The radiogram was unsatisfactory because the solution spread beyond the confines of the bronchial tree, invading the parenchyma.

[1] Read before the Section on Medicine, New York Academy of Medicine, November 18, 1919.

[2] Jour. Am. Med. Assn., vol. xlv, p. 178.

[3] Arch. Int. Med., April 16, 1917, p. 538.

A second dog injected with a small quantity of thorium survived until the following morning. When the lungs at postmortem were injected with barium in acacia they showed details of lung structure

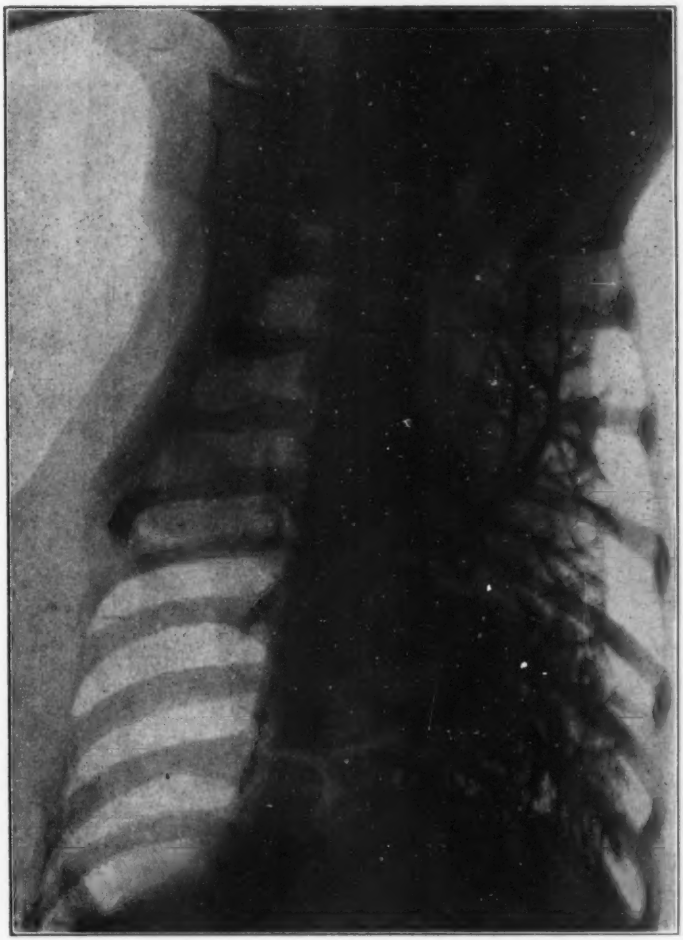

FIG. 1.—No. 8. October 16, 1919. Black and white fox terrier, five and a half minutes after injection of 1 mil. of adrenalin chloride. Dog had received 10 c.c. of barium in olive oil suspension. The terminal bronchi are contracted.

as far as the alveoli and served to visualize the conception of lung structure very much as do corrosion specimens.

The lungs of a fourth dog were injected with barium in gelatin

after chloroform anesthesia, using the formula employed by Louis Gross in his injections of the vascular trees of excised organs. This experiment gave pictures which were too indefinite for satisfactory study, and the dog so injected died of a pneumonia involving the area injected six days later. This was attributed to a decomposition of the gelatin.

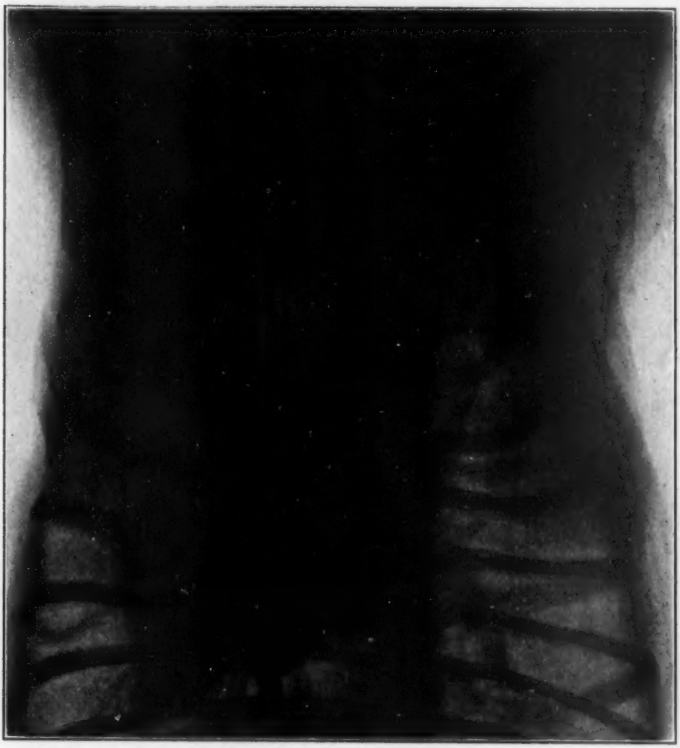

FIG. 2.—No. 9. October 18, 1919. Black and white fox terrier after injection of adrenalin, in deep inspiration.

It was now decided to employ a medium which would not putrefy and which could readily carry a larger amount of barium. It was felt that iodoform poisoning had probably contributed to the death of the dogs in the Waters, Bayne-Jones and Rowntree experiments. Barium sulphate was triturated with anhydrous olive oil until a thick, smooth paste was formed. This paste was injected into anesthetized dogs directly into a bronchus in amounts of 5 to 10 c.c., depending upon the size of the dog. In one dog barium was tri-

turated with liquid petrolatum to form a thick paste. This was as satisfactory as the olive oil, and more readily sterilized. Only one of the dogs has died. Our dogs have been reinjected at an interval of three to seven days. In one dog the experiment was repeated twice in the same evening, when it was found that the lung had emptied itself after an hour. So far in our experiments the procedure

FIG. 3.—No. 10. October 18, 1919. Black and white fox terrier after injection of adrenalin, deep expiration. Note that ribs are elevated and bronchi are narrow in contrast to appearance in No. 9.

seems relatively innocuous in healthy dogs. One small dog which was injected with a large amount of barium in oil, retained sufficient in the right lower lobe to cast a shadow, which radiographically simulated a pneumonia for several weeks. After four subsequent injections the dog wasted away and finally died. A roentgen ray

of the lung shows a general filling of the alveoli with barium. The external surface of the lung appeared white in places.

The dogs were studied fluoroscopically and radiographs were taken. Most of the dogs tolerated these injections excellently.

Under the fluoroscope we have studied the movements in the bronchi and have observed the following phenomena:

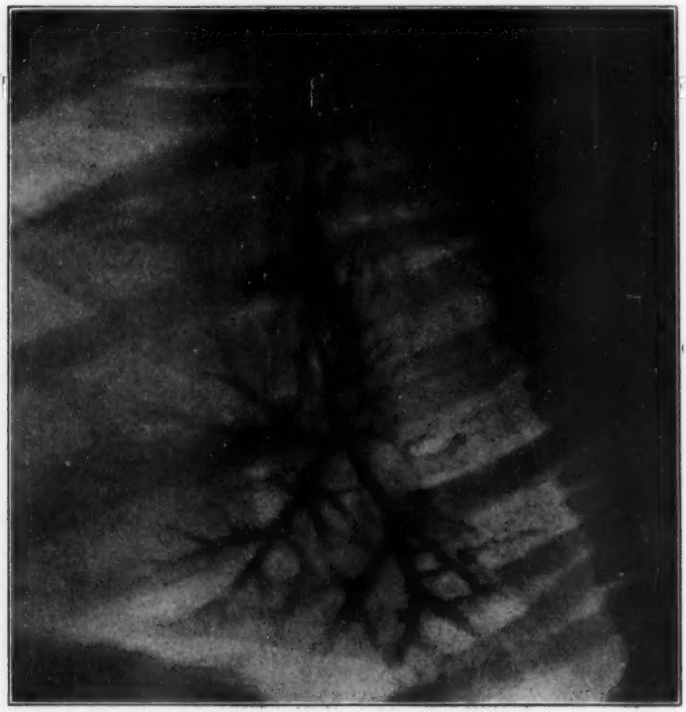

FIG. 4.—No. 15. October 28, 1919. Male brindle pup anesthetized with ether, 10 minims of adrenalin chloride; five minutes later, 5 c.c. of barium in oil, which went into the stomach; ten minutes later, 10 minims of adrenalin chloride; then tracheal injection of 10 c.c. of barium in oil; immediate plate. Terminal bronchi are spastic so that barium may not enter.

1. If the left diaphragmatic bronchus and its branches are injected it is seen to move laterally with each pulsation of the heart.

2. There is, synchronous with respiration, a bellows-like expansion and contraction of the trachea and bronchi, which is very obvious in the relaxed bronchus immediately after injection, and especially if the anesthetic has not completely worn off (Figs. 2 and 3).

This expansion and compression of the bronchi is probably produced by costal breathing and the suppression of this bellows-like

action when movements of the ribs are limited may have deleterious effects. It seems possible to infer, from our observations, that the spastic contraction of the bronchus is as important in limiting the expansibility of the lung as it is in diminishing the caliber of the bronchi. Observations on chronic stenosis of the larynx at the Willard Parker Hospital by one of us (J. G. M. B.) have established

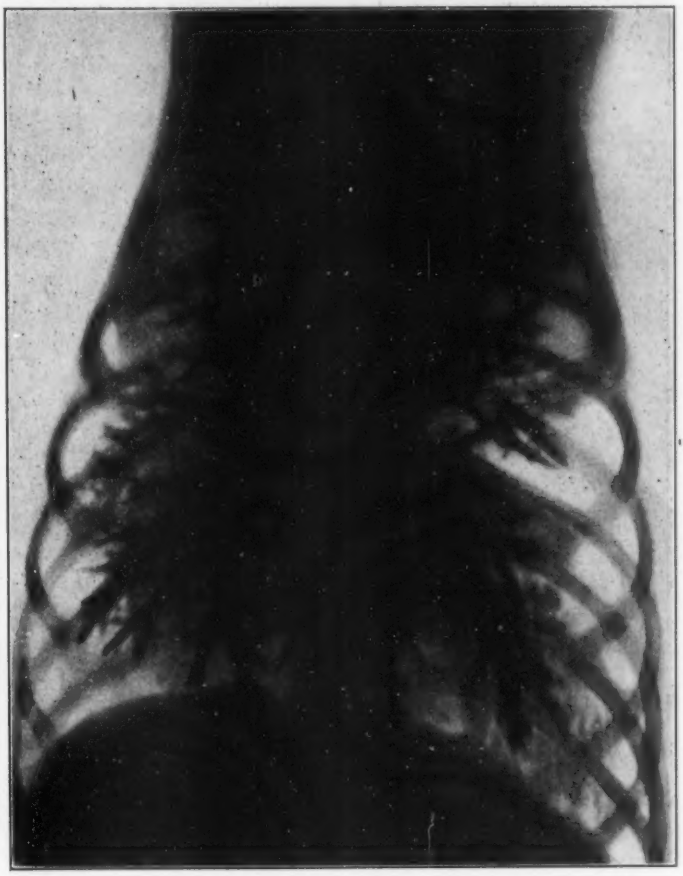

FIG. 5.—No. 16. October 28, 1919. Adrenalin given before tracheal instillation of barium. Terminal bronchi contracted and not filled.

the fact that a reduction in the tracheal lumen to one-third its size does not interfere with adequate respiration. Our observations may prove important in explaining the pathology of bronchiectasis and

recall von Basch's views on the importance of lost distensibility in the production of asthma and emphysema.

3. In addition to the two movements of the bronchus mentioned a third movement of larger cycle was observed. This is a movement

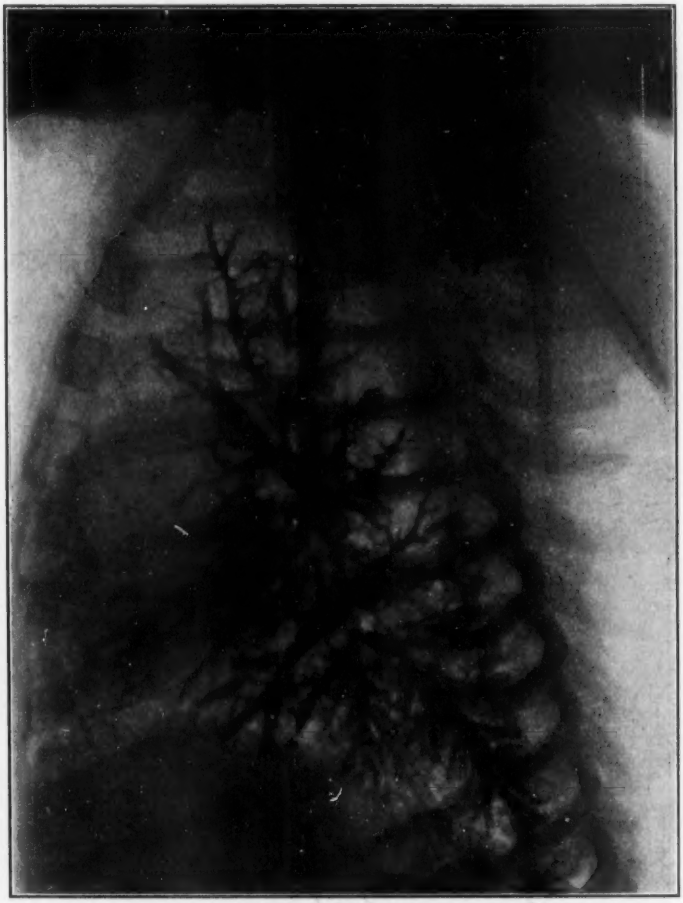

FIG. 6.—No. 18. October 28, 1919. Peristaltic movement of trachea, and bronchi; lateral view.

of long peristaltic wave (10 cm.), though its amplitude is small. It is visible immediately after the injection of barium, and seems to be a potent factor in the evacuation of the bronchi and trachea. It is readily seen if a given point in the bronchus is kept under observation, at this point the bronchus or trachea is seen to contract and dilate

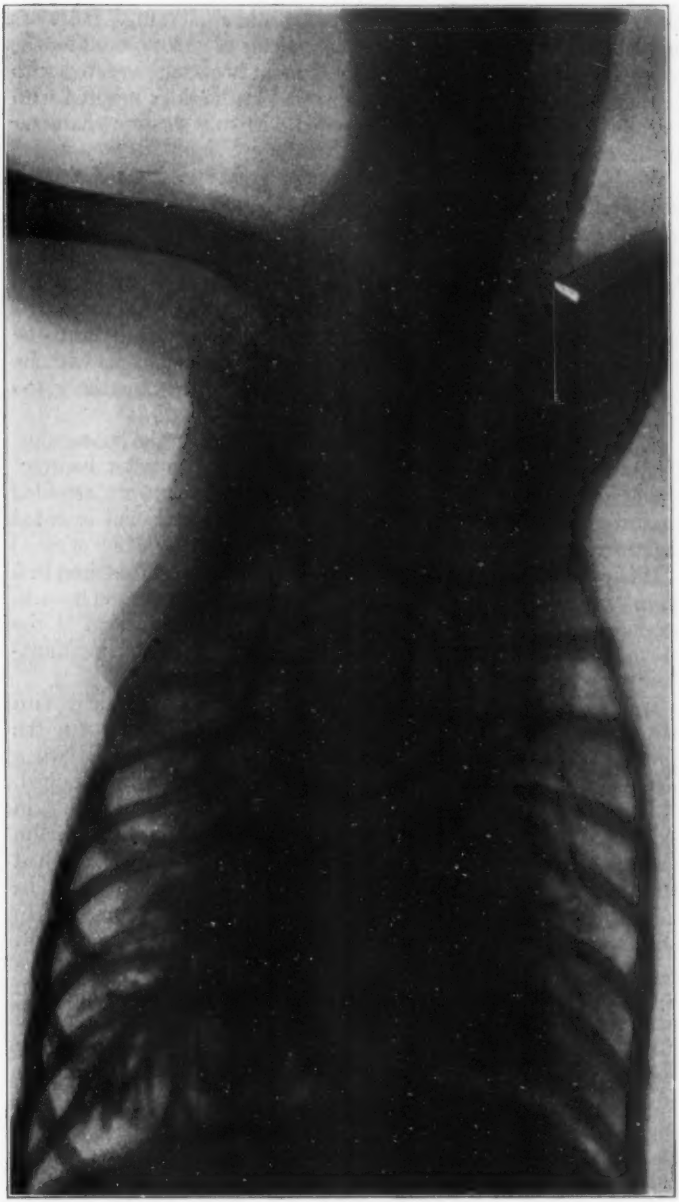

FIG. 7.—October 28, 1919. Same conditions on very rapid plates demonstrating peristaltic wave in trachea and bronchi; anterior view.

slowly, independent of cough, respiration and swallowing. It travels up the bronchial tree. This movement seems to us to account for the wave-like structure observed in the human bronchus injected with barium in acacia and also to be revealed in the dogs injected with barium paste, and may be contrasted with the sac-like character of the excised injected bronchi.

We submit a plate (Fig. 7), taken with great speed, which reveals sharply this peristaltic wave. We regret there is no available method of radiographic cinemetography, so that these movements may be analyzed more accurately. The lungs seem to empty themselves largely by means of this peristaltic movement, for even when the dogs are held upright so that gravity which readily empties a dog's lung cannot act, successive masses of the injection are seen to be expelled from the larynx and to travel down the esophagus without evidence of accompanying cough. This movement is entirely too rapid to be attributed to ciliary action.

4. We have also studied bechic movement under the fluoroscope. Under their influence the chest and abdominal muscles contract simultaneously, so that the lung and bronchial branches are crowded toward the trachea. These branches are shortened and crowded together.

It is probable that the air contained in the alveoli is expired in a more concentrated blast. Under the influence of cough the bronchi are emptied more rapidly. It is possible that contraction of the bronchial muscles directly influences by traction or nervous stimulation the contraction of the chest parietes.

We injected adrenalin in dogs after filling their bronchi with barium and hoped to see the bronchi dilated. To our surprise the bronchi appeared smaller. Notwithstanding the fact that when pictures were taken, the same phase of respiration was obtained, as shown by the position of the ribs. This observation is not in accord with that accepted as the physiological action of adrenalin on bronchial muscles. At first it was thought that the lung had emptied itself in the interval allowed for the adrenalin to act. In order to avoid this confusing factor, adrenalin was administered to a dog before the barium was injected. We obtained the same result. In one dog adrenalin caused an increased rate of emptying of the bronchus with coughing. In another dog after giving benzyl-benzoate, which is alleged and was observed to cause bronchial dilatation, adrenalin was given and the bronchi were found to be contracted. In another dog bronchial spasm was induced by administering 1 mg. of muscarin intravenously. This was associated with considerable coughing and persistent general muscular twitching. An intravenous dose of adrenalin relaxed the spasm of the bronchi and caused the twitching to disappear. (See illustrations.)

We are aware of the shortcomings and paucity of our observations, but we have concluded to report them, with the conviction

that the observations contribute to a more correct understanding of the physiology of the bronchi.

In conclusion we have observed:

1. A bellows-like action in the trachea and bronchi which may be limited by contraction of the bronchial muscles.

2. A peristaltic action of the bronchial muscles, which seems adequate to empty them without invoking ciliary movement.

3. The action of adrenalin, benzyl benzoate, ether and muscarin have been observed by this roentgen-ray method.

The writers wish to record their debt to Dr. William B. Giles and Dr. Louis Griessman for valuable assistance and collaboration.

HETEROPLASTIC BONE FORMATION IN THE FALLOPIAN TUBE.

By Goichi Asami, M.D.,

HONOLULU, H. I.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine, Saint Louis, Missouri.)

In the course of a routine examination of tissues recently removed at operations on the gynecological service of the Barnes Hospital, my curiosity was aroused by the difficulty which I encountered in attempting to cut a block of tissues from a Fallopian tube. Upon a closer inspection what appeared to be a spicule of bone, about 5 mm. wide and less than 1 mm. thick, was seen to protrude from the cut end of the tubal lumen. There were several other foci of similar resistance in the wall of the tube and in the mesosalpinx.

Presentation of the Case. The patient, M. J., a negress, aged thirty-seven years, was admitted to the gynecological service of the Barnes Hospital with complaints of a pain in the left lower quadrant and a firm mass in the lower abdomen. The family and past histories were unimportant. Menstruation started at the age of thirteen, and has been always regular, recurring every twenty-eight days and lasting from seven to twelve days. The flow has been rather profuse as a rule. The patient has not missed any period except in connection with her pregnancies. She has had intermenstrual bleedings for the past three years. The last menstrual period started on August 24, 1919 and was still continuing at the time of admission, September 14. The patient has had three pregnancies, two of which were full term and one a miscarriage. The oldest child is twenty years old and the miscarriage occurred ten years ago. The present illness dates back for three years, with an aching pain in the left lower quadrant. The pain was constant, and on several occasions during

the past three years the patient was compelled to take to bed for two or three days at a time. The hard lump in the lower abdomen was noticed only two months ago. General physical examination showed a fairly well-nourished colored woman in good health. Abdominal and pelvic examination revealed a spherical tumor mass which occupied the pelvis and the lower part of the abdomen, and was connected with the uterus. A diagnosis of uterine myoma was made and a laparotomy was performed by Dr. H. S. Crossen on September 18, 1919. At the operation the following notes were made:

"Mid-abdominal incision. Uterus is enlarged to the size of a grape-fruit, with fibroids. Both tubes are enlarged and distended with fluid. The left ovary appears normal. The right ovary is enlarged and chronically inflamed. Many adhesions are seen around the adnexa. The supravaginal portion of the uterus, both tubes and the right ovary removed. There is a calcified nodule of the size of a bean in the ovary."

The specimen was brought to the Laboratory, September 18, 1919, and was numbered, Gynecological Pathological No. 1288.

Gross Description of the Specimen. The formalin fixed specimen consists of the oval-shaped, supravaginal portion of the uterus, the left tube and the right tube and ovary. The uterus measures 13 x 11 x 8 cm. It is roughly of the size and shape of a grapefruit. It is covered on its surface with shaggy, loose fibrous tissue, which is grayish white in color. On cutting it open the dilated uterine canal is seen to contain a dark, grayish mass, measuring 8 cm. in its longest diameter. It is shaped like an alligator pear, with its superior and inferior axis elongated. The mass tapers gradually toward the lower end of the uterine canal; it is soft and pliable in consistency and it is attached to the uterine wall by means of a thin, fibrous band.

Both tubes are dilated and tortuous. The left tube measures 8 cm. in length. In its proximal third the organ retains its normal size and appearances. In the distal two-thirds it is dilated into a cyst-like sac whose greatest diameter is 3 cm. Its wall is as thin as parchment, it is semitransparent and it sends off several septa, thus converting the interior of the sac into several separate chambers. The contained fluid is colorless and watery.

Many loose fibrous adhesions pass between the right tube and ovary. The ovary measures 4 x 3 x 2.5 cm. The tube measures 7 cm. long, 1.5 cm. in transverse diameter close to the uterine cornua and 1.2 cm. throughout the rest of its length. In the mesosalpinx close to the tube there is a point at which the cutting knife meets with a considerable resistance. Similar resistance is encountered in the entire length of the tube except close to the uterine cornua. On the cut surface the tubal lumen shows a spicule of bone about 5 mm. wide and less than 1 mm. thick, firmly embedded in the substance

of the tube. The wall of the tube and the mesosalpinx also contain many small bony areas. The ovarian tissues do not seem to contain any trace of bone-like material. The ovary and the tube were cut together into several blocks about 1 cm. thick, decalcified in phloroglucin and nitric acid, embedded in celloidin, several sections being cut from each block.

Microscopic Description. The uterine tumor proved to be a myoma which has undergone hyaline degeneration in many places. The left tube was chronically inflamed. The right ovary appeared normal except for a chronic perioöphoritis, and showed no calcified or ossified areas.

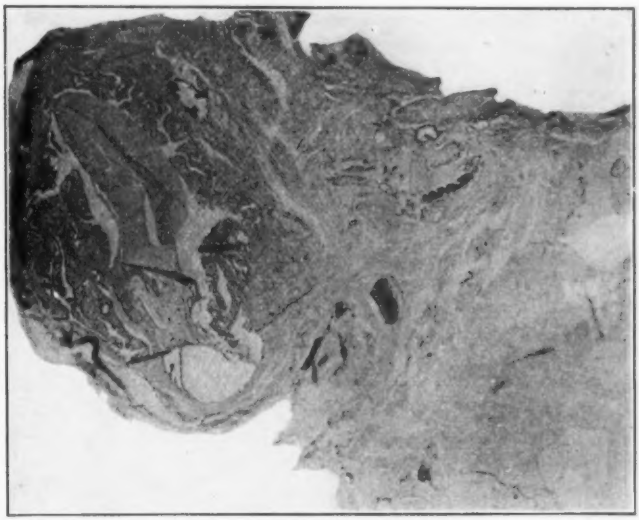

FIG. 1.—A section of the entire tube and a portion of the ovary is shown. The ovary appears normal. In the mesosalpinx, in the upper portion of the section, there are several black streaks and dots which represent bony and cartilaginous islands. Calcium deposits that are located in this region are not visible. In the wall of the tube (lower portion of the section) there are several similar streaks. In the lumen of the tube will be seen a less deeply stained bony bar surrounded by hyaline connective tissue.

In the mesosalpinx between the right tube and ovary there are several foci of intense lymphocytic infiltration. In this same area the bloodvessels also are numerous and are distended with blood. In the small area midway between the ovary and tube there are several points at which the connective tissue is somewhat denser than elsewhere, and it is in these connective-tissue areas that the bony spicules occur. Close to some of these bony spicules are also seen some islands of cartilage (Fig. 1).

One of these cartilaginous islands which is included between two parallel rows of bone has certain peculiarities. On one of its sides there is a slender bar of bone having a somewhat serrated outline and containing in its substance much minute, deep blue: staining material resembling closely the cartilaginous tissue. Along its outer borders are a small number of osteoblasts. On the opposite side of the cartilage there are three separate bars of bone, each somewhat more slender than the one just described and much shorter (Fig. 2). These bony bars are separated from one another by somewhat hyaline connective tissue which contains scant, fusiform nuclei. The cartilage enclosed between these rows of bones is composed of

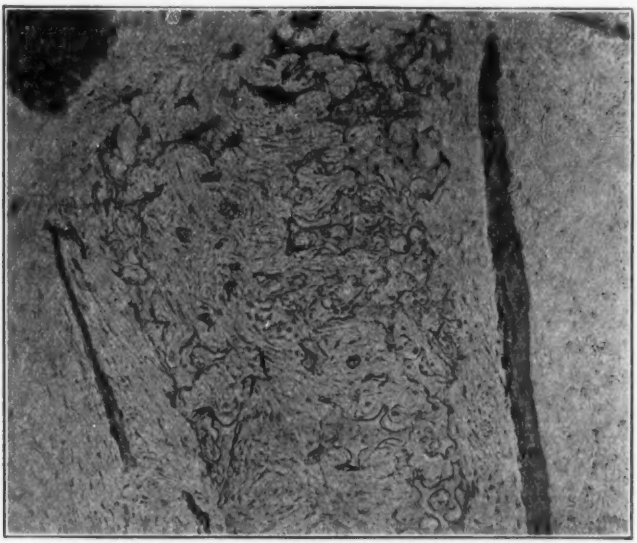

FIG. 2.—Numerous islets of cartilage are apparently undergoing destruction, and are surrounded by connective tissue. A fraction of bone is shown on either side of this cartilage. These bones contain deeply stained remnants of cartilage.

numerous minute islets of pale blue staining, irregularly outlined tissue, which contains here and there cells resembling plasma cells. These cartilaginous islands are of various sizes and appear decidedly porous, as the result of the presence of numerous variously sized cavities in their substance. Some of these cavities are apparently closed cavities and others mere indentations along the border. In these cavities and indentations there is often seen reticular connective tissue containing many clear vacuoles which resemble fat spaces. It also contains capillaries filled with erythrocytes and lymphocytes. The connective tissue in these indentations is continuous with that lying without, and contains a moderate number of capillary

vessels. The indentations above mentioned are decidedly angular in shape and thus give the impression that the cartilage might be in the process of destruction. The fibrous connective-tissue cells in this region and in the indentations are slender and contain moderately numerous, slender, fusiform nuclei, and appear rather young. In this neighborhood, where erythrocytes are found in a great number, apparently free in the connective tissue whose cells appear to be young fibroblasts in the process of organization, there are seen several foci of calcific deposits. These deposits are in the form of minute rings which surround a mass of erythrocytes in some instances and a hyaline mass of what appears to be fibrous tissue in other instances. In still other instances they consist of solid, spherical masses. These evidently represent a calcification of small vessels and capillaries which have undergone a hyaline thrombosis. Some of the larger deposits show under a higher magnification cells which possess radial processes, very much like bone corpuscles. Osteoblastic cells are not readily made out in connection with these calcific deposits, except in some few instances.

Other cartilaginous islands are also closely associated with osseous tissue and show deposits of calcium salts which on section appear as deeply blue-stained granules. At this calcified area the cartilage cells have lost their outline entirely and are converted into a single area surrounded by ossified tissue. Around these ossifying cartilages erythrocytes are found in a large mass as if a hemorrhage may have occurred. The connective tissue on the whole is hyaline here. A definite lymphocytic infiltration is also noted (Fig. 3).

In this area one also meets with a few gland-like structures lined by a low cuboidal epithelium. Immediately beneath this epithelium are found some lymphocytes. Some minute ossified nodules impinge upon the epithelium from underneath and at some points push it out into the gland-like lumen. Some of these nodules are definitely associated with cartilage, others evidently independent, but both are surrounded by lymphocytes and osteoblasts.

The wall of the tube contains numerous foci of ossification which are more or less continuous with the area above described, no definite line of demarcation being visible. These foci differ very little from the description given above.

The mucosa of the tube presents an almost normal appearance except that the submucous connective tissue contains numerous capillaries which are filled with a large number of polymorphonuclear leukocytes, both neutrophilic and eosinophilic. This connective tissue is also infiltrated with lymphocytes and appears definitely hyaline. There are a few foci of ossification in the submucous connective tissue. These bone spicules also contain in their substance deeply blue-stained material.

The continuity of the mucosa of the tube is interrupted at two opposite poles of its lumen by a rather broad band of tissues con-

FIG. 3.—Cartilage is undergoing ossification. Swollen cartilage cells, granular calcium deposits and new-formed bone are to be seen.

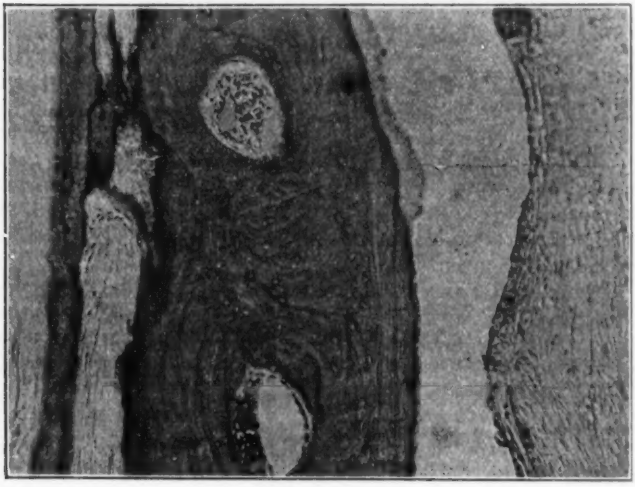

FIG. 4.—One of the bony bars found in the tubal lumen is shown. There are two typical Haversian systems.

taining two spicules of bone (Fig. 1). The lining on either side of this band is directly continuous with the epithelium of the tubal mucosa, and is composed of flattened cells. The band shows a well-formed bony bar which contains a moderate number of healthy corpuscles and a few typical Haversian canals. This bone is also covered with a few osteoblasts. Immediately outside of this osteoblastic membrane the connective tissue is loose and contains a number of fat vacuoles. Another bar of bone is arranged almost in a parallel direction to the one just described. This bone is located close to the tubal mucosa and is considerably smaller than the other. These two rows of bone enclose between them thick layers of connective tissue which contain delicate, fusiform nuclei, lymphocytes and fat vacuoles (Fig. 4).

Between the larger bone spicule and the lining of the "band" there are thick layers of hyaline tissue the elements of which consist of long, parallel, fiber-like structures which are very poor in nuclei and thus qualify for the so-called osteoid tissue (Fig. 1). Intimately mixed with this osteoid tissue are a few minute pieces of bone surrounded by a few osteoblast-like cells. Toward the portion of the mucosa where its continuity is broken by the band of tissues above described the connective tissue appears more like normal except for lymphocytic infiltration.

In short, the Fallopian tube presents a picture of a definite chronic inflammation of its fibromuscular wall and the mesosalpinx, in which are several foci of cartilaginous tissue undergoing a degeneration both alone and accompanied by ossification. There are in the mesosalpinx, close to the tube, definite evidences of calcific deposition which has involved arterioles and capillaries that have undergone a hyaline thrombosis. Cartilage is here seen to be in an actual process of ossification, in which process the area ahead of ossification is a seat of deposition of granular calcium salts and of the disappearance of the outline of the cartilage cells. Thus swollen and irregular cartilage cells are seen lying within the ossifying cartilage, a part of which has been calcified. The bone found in this case varies from a well-formed one with typical Haversian systems of a sort of marrow spaces to an incompletely developed bar still containing remnants of cartilaginous tissue. The bone, in addition to its association with degenerating cartilage, is seen to lie free in the osteoid tissue independent of either cartilage or calcific deposit. Such a bone, however, contains in its substance what has been described as the remnants of cartilaginous tissue.

Discussion. Numerous cases of aberrant bone production have been recorded in the literature. The majority of these cases have occurred in the cardiovascular system in connection with sclerosis and calcareous degeneration. Howse,[1] Marchand,[2] Paul,[3] Rosen-

[1] Tr. Path. Soc., London, 1877, vol. i. [2] Eulenberg's Real-Encyklopaedie, 1885.
[3] British Med. Jour., 1885, vol. xxviii.

stein,[4] Kryloff,[5] Schroetter,[6] Roehmer,[7] Moenckeberg,[8] Thorel,[9] Bunting,[10] Harvey,[11] and Buerger and Oppenheimer[12] and others have contributed to the literature dealing with this subject. Zanda,[13] Cruveilhier,[14] and others have reported an occurrence of bone in the cerebral meninges; Pollack[15] and Poscharissky[16] in the lymph nodes; Morpurgo[17] in the bladder mucosa; Laboulin,[18] Huartado[19] and Pollack in the pleura; Ponfick,[20] Roepke[21] and many others in the muscle; Pollack in the calcified uterine myoma; Cornil and Ranvier[22] in the liver; Ribbert[23] in the suprarenal capsule; Klebs,[24] Knapp[25] and others in the eye; Adachi,[26] Outerbridge[27] and others in the ovary, and elsewhere.

Theoretical considerations of the heteroplastic bone formation have been given much prominence by various authors, notably von Hansemann, Ribbert, Bunting, Buerger and Oppenheimer and Pollack. The contentions of these authors may be summarized as follows:

1. Embryonic misplacement after the hypothesis of Cohnheim.
2. Metaplasia of connective tissue after the manner of callus formation.
3. Erosion of calcific deposit with the formation of vascularized spaces containing young connective tissue which assumes the role of osteoblasts.

Bunting disposes of the hypothesis of embryonic misplacement on the ground that the occurrence of the aberrant bone formation is too frequent to be explained on such a basis, that the bone formation occurs in connection with sclerosis and calcareous degeneration and that the experimental production of aberrant bone as carried out by Barth,[28] Sacerdotti[29] and Frattin has demonstrated that when a favorable condition exists which gives a proper stimulus to young connective-tissue cells the metaplasia of these cells into osteoblasts can occur. This proper stimulus is assigned by Bunting to calcium salts present in the lime deposits. The metaplasia theory is further supported by the fact that in practically all the cases

[4] Virchows Arch., 1900, vol. clxii.
[5] Cited by Poscharissky.
[6] Nothnagel's Handbuch, 1901, vol. xv.
[7] Virchows Arch., 1901, vol. clxvi.
[8] Virchows Arch., 1901, vol. clxvii.
[9] Ergebn. d. allg. Path. u. pathol. Anat., 1904, vol. ix.
[10] Jour. Exp. Med., 1906, vol. viii.
[11] Jour. Med. Research, 1907, vol. xviii.
[12] Jour. Exp. Med., 1908, vol. x.
[13] Ziegler's Beitr., 1889, vol. v.
[14] Traite d'anat. pathol. general, 1894.
[15] Virchows Arch., 1901, vol. clxv.
[16] Ziegler's Beitr., 1905, vol. xxxviii.
[17] Cited by Poscharissky.
[18] Idem.
[19] Idem.
[20] Cited by Buerger and Oppenheimer.
[21] Langenbeck's Arch., 1907, vol. lxxxii.
[22] Manuel d'histologie pathol., 1901, vol. i.
[23] Geschwülstlehre, 1904.
[24] Pathological Anatomy, vol. i.
[25] Arch. f. Aug. u. Ohrenheilk., 1871, vol. ii.
[26] Zentralbl. f. allg. Pathol. u. path. Anat., 1913, vol. xxiv.
[27] Am. Jour. Med. Sc., 1916, vol. cli.
[28] Ziegler's Beitr., 1895, vol. xvii.
[29] Virchows Arch., 1902, vol. clxviii.

reported in the literature the bone has been formed in young proliferating connective tissue in the neighborhood of calcific deposits.

As regards the cause of invasion by the young connective tissue and bloodvessels, Paul has suggested a trauma such as a fracture of calcific plates. Bunting upholds this suggestion and cites Howse's case of ruptured axillary artery, and Cohn's case of traumatized crural artery, and presents his own case in which signs of hemorrhage and old inflammatory exudates were found as supporting evidences in favor of this view.

The metaplasia theory encounters a few opponents, among whom Ribbert and von Hansemann[30] may be mentioned. Ribbert, in his monograph on tumors, states that metaplasia of connective tissue into bone occurs only when there have been cells belonging to the osseous system, and therefore such a change is not a metaplasia in the strict sense of the word. Von Hansemann believes that the aberrant bone originates in the misplaced islands of cartilage or perichondrium.

Whether or not the bone found in the thyroid, breasts, eye and elsewhere in the structures which are contiguous with cartilage originates in accordance with Hansemann's view cannot be definitely decided, but such a mode of bone formation so frequently to be encountered in the lung, in the liver, and in the arterial walls cannot readily be conceived. Such is the stand taken by the supporters of the metaplasia theory as regards the contentions of Ribbert and von Hansemann.

Two views are supported by Bunting as regards the mode of metaplasia involved in aberrant bone production, namely: (1) there may be a direct metaplasia of connective tissue into osteoid (callus) tissue with subsequent conversion into bone, and (2) resorption of calcific material by bloodvessels and young connective-tissue cells, formation of bone marrows and deposition of bone in the periphery by an osteoblastic membrane derived from the metaplasia of the connective-tissue cells accompanying the vessels.

In Bunting's case a cellular marrow was found. This contained mononuclear cells of myelocyte type, many of which with eosinophilic granules, polynuclear cells, both eosinophilic and neutrophilic, lymphoid cells and cells of erythrocyte series, non-nucleated cells and normoblasts. Thus the marrow space described by this author corresponds closely to the normal bone-marrow. These elements of bone-marrow are attributed by Bunting either to a metaplasia of the connective-tissue cells or to a metaplasia of the emigrated cells from the blood stream which are capable of further differentiating into various types of cells.

In 1907 Harvey experimentally produced bone in the rabbit's aorta by an application of irritants to its wall. Here again the cal-

[30] Berl. klin. Wchnschr., 1900, vol. xxxvii.

cific deposits were found to be closely associated with the production of bone.

Buerger and Oppenheimer, in 1908, reported a case of multiple bone formation in the sclerotic arteries and discussed at length the various features of heteroplastic bone formation. They follow Cohn, Pollack, Moenckeberg and Bunting in upholding the theory of metaplasia, but differ from Paul and Bunting in maintaining that the proliferation and invasion of the young connective tissue are brought about not only by trauma, but may occur in connection with organizing thrombus, canalization and vascularization of obliterating intima and the disease of the media. They further pointed out that in their case, at any rate, the cartilage was never transformed into bone.

In his recent monograph on neoplasms Ewing[31] mentions a certain alteration in calcium metabolism as one of the causative factors in heteroplastic bone formation. In fact, Thayer and Haven[32] have recently reported a case in which an excessive intake of calcium resulted in a deposition of calcium salts at the site of a chronic inflammatory lesion of the breast.

In the present study the abundance of degenerating cartilage and an evidence of endochondrial ossification first suggested a possibility of a previous tubal pregnancy, with subsequent absorption of all the embryonic tissues except cartilage. The clinical history is negative as regards this possibility. Even if it be assumed that the patient's own account of her previous history was inaccurate and that the tubal pregnancy had, indeed, occurred, it is certain that this pregnancy could not have taken place later than at least three years ago. The myoma which has occupied the uterine canal and has caused an intermenstrual bleeding for the past three years would have prevented an impregnation from taking place later than the onset of the present illness. It is inconceivable that even a cartilage could have remained preserved for this length of time. Although circumstances may differ in some respects, an observation made by Barth that a piece of bone introduced into the peritoneal cavity of the rabbit has been partially absorbed within six weeks' time is of some significance in this connection. Furthermore, the distribution of cartilage and bone found in this case involves practically the entire circumference of the tube. Such a distribution also is an argument against the hypothesis of the fetal remains. Finally, the presence of the osteoid tissue in conjunction with bone suggests that there has been a bone-formation independent of the cartilage.

Von Hansemann's theory on the origin of the heteroplastic bone appears here untenable. To assume that during the embryonal life a perichondrium or cartilage has been misplaced in such a

[31] Neoplastic Diseases, 1919.
[32] Jour. Exp. Med., 1907, vol. ix.

manner as to make it lie dormant in the Fallopian tube is merely hypothetical. Furthermore, it seems impossible that either perichondrium or cartilage, or any single tissue for that matter, can alone be involved in the process of embryonic misplacement.

The facts observed in this case, that in the capillary area of the mesosalpinx there are still left several foci of calcific deposits in the small bloodvessels which have undergone a hyaline thrombosis, and that in this area there are evidences of hemorrhage and chronic inflammatory reaction, and in addition that there are bone spicules formed in the osteoid tissue suggest that a transformation of the connective tissue into osteogenetic tissue has occurred. It is further probable that most of the calcific deposits have been resorbed in the process of metaplasia some time previous to the date of the operation.

At this point it seems advisable to define the use of the term "metaplasia," since there is a considerable confusion among the authorities. The term as it is applied in this communication is an extension of the definition given by Orth, namely, a transformation of one differentiated tissue into another differentiated tissue *either directly or indirectly through the medium of a less differentiated form of the original tissue.*

The presence of cartilaginous tissue, which in no place is entirely healthy but shows either more or less retrograde changes or ossification, and its close association to many of the young bones found in this case, seems to point to a primary metaplasia of connective tissue into cartilage, with a subsequent conversion into bone. Thus there seem to be two distinct processes involved in the formation of bone. On the one hand, there may have been a resorption of calcific deposits by the proliferating connective-tissue cells and bloodvessels which have invaded the calcified area in the course of inflammatory reaction, the conversion of the connective-tissue cells into bone-forming cells and the deposition of osteoid tissue by these cells. On the other hand, there may have been a metaplasia of the connective-tissue cells into chondrogenetic cells and a subsequent endochondral ossification.

By what mechanism a connective tissue may be transformed into cartilage cannot be made out in the present case, since there has been no new forming cartilage to be found. It is also uncertain as to how the process of the ossification of cartilage may have been initiated. Whether the disintegrating cartilage cells might become osteogenetic or not is impossible to say. Geddes[33] has stated that in many respects cartilage cells cannot be differentiated from osteoblasts. This point plainly needs a further experimental investigation.

[33] Jour. Anat. and Physiol., 1912, vol. xlvii.

Summary and Conclusion. 1. A case of aberrant bone formation in the Fallopian tube is presented.

2. Both cartilages undergoing ossification and calcific deposits, with surrounding organization tissue, some of which has been converted into an osteoid tissue are present.

3. Metaplasia of connective tissue into bone, both with the formation of cartilage and with the production of osteoid tissue is assumed to have occurred.

4. The possible mechanism involved in the conversion of the connective issue into cartilage and of the cartilage into bone is left for a future experimental investigation.

MERCURY BICHLORIDE INTRAVENOUSLY.[1]

By Carl H. Bastron, A.M., M.D.,
LINCOLN, NEB.

The intravenous administration of mercury bichloride is a comparatively recent method of treatment. Osler gives it passing mention in the eighth edition of *Principles and Practice of Medicine* (1914) under the treatment of Syphilis. Baccelli, of Rome, began using it in 1917 in the treatment of gonorrheal arthritis, claiming excellent results. Within more recent years mercury salts have been advocated for intravenous injection in syphilis by R. L. Spittel, of England,[2] and E. F. Sanz, of Spain;[3] in the treatment of enlarged spleen due to chronic malaria by Greig and Ritchie of Calcutta, India;[4] in influenza by G. Ferrarini, of Italy;[5] in puerperal septicemia by J. A. Perez,[6] of Spain, in gonorrheal arthritis, erysipelas, influenza, anthrax and pyelitis, by Victor G. Vecki, of San Francisco.[7]

The technic of injecting mercury bichloride intravenously is very simple. The mercury bichloride is dissolved in normal salt solution, 10 c.c. of the solution containing 1 grain of the drug. The bichloride solution may be kept in a glass-stoppered bottle or it may be distributed in ampoules in amounts of 1, 2, 3, 4 and 5 c.c. each. Treatment is begun with 1 c.c. of the solution, which contains gr. $\frac{1}{10}$ mercury bichloride. A tourniquet is applied above the elbow, the skin over a prominent vein is cleansed, the needle, preferably a fine, long, platinum needle is carefully introduced, so that the point rests free in the lumen; the tourniquet is now removed and the solution

[1] Read before the Lancaster County Medical Society, October 18, 1919.
[2] Practitioner, London, October, 1918, p. 212.
[3] Medicina Ibera, Madrid, August 17, 1918, p.187.
[4] Indian Jour. Med. Res., Calcutta.
[5] Riforma Medica, Naples, November 9, 1918, p. 893.
[6] Medicina Ibera, Madrid, August 3, 1918, p. 130.
[7] Jour. Am. Med. Assn., May 31, 1919, p. 1596.

injected slowly. The needle is then withdrawn and the solution hastened through the vein by the patient raising his arm over his head and alternately closing and opening his fist.

Advantages claimed for this method over the other modes of mercury administration are that quicker results in treatmenf are obtained, a more accurate grading of dosage is made possible, and the course of the disease can be more closely observed, since the patient is seen oftener than is the case with other methods of treatment, and in the case of syphilis, frequent opportunity is given to obtain blood for the Wassermann reaction.

The intravenous injection of mercury bichloride is a comparatively safe procedure, and altogether painless and free from alarming reactions, immediate or late, provided certain very simple precautions are observed. One of these is that the needle should enter the vein and its point lie free in the lumen of the vein before injection is begun. This is to avoid injecting the drug outside the vein or into its wall and thus guard against the chief objection to this method, namely, pain at the site of injection and occlusion of the vein by a thrombus. Another precaution is that of using dilute solution of mercury bichloride. Concentrated solutions often cause a spasmodic contraction of the wall of the injected vein and a permanent occlusion of its lumen. Dr. H. S. Newcomer, of Philadelphia,[8] describes this condition in connection with arsphenamin injection: "There is a local reaction of the veins used for injection, which is fairly common. . . . Sometimes when one is injecting salvarsan into a vein which lies for a considerable distance superficially in the skin, the vein will be seen to contract throughout its entire length and become like a whipcord. The salvarsan ceases to flow and the condition continues for some time. Under some circumstances this contraction remains and is followed by thrombosis. The thrombosis may occur without the contraction having been superficially noticed. . . . Localized thrombosis certainly sometimes occurs, due to injury to the vein, because of faulty technic; but the reaction undoubtedly occurs when the injury to the veins is out of question, when the vein is large and free and the needle small and sharp. It occurs more frequently as the NaOH in the salvarsan is increased. It is more common in colored people than in white people." Another precaution to be observed is that of using a small needle; a one-inch gauge 25 platinum needle serves the purpose well. A large needle causes more pain, enters the vein with more difficulty and causes more injury to the vein. One more precaution. Treatment should be begun with a small dose, not over gr. $\frac{1}{10}$ of the drug, and increase should be gradual and cautious. The injections can be given as often as once a day, but an injection every other day or three times a week is safer. This is continued

[8] Am. Jour. Med. Sc., August, 1919, p. 159.

until signs of mercurialism appear, when the injections are reduced to one or two a week.

The routine I have been following for some time in cases of syphilis is to give the mercury bichloride injections three times a week, starting with gr. $\frac{1}{10}$, giving gr. $\frac{3}{20}$ to gr. $\frac{2}{10}$ the second dose, gr. $\frac{2}{10}$ to gr. $\frac{1}{4}$ ($\frac{5}{20}$) the third, and gr. $\frac{3}{10}$ the fourth. In the case of a strong man the dose can be thus gradually increased to gr. $\frac{1}{2}$. As soon as signs of saturation appear, usually a slight soreness in the teeth if the jaws are shut with a snap, it is considered that the maximum dose for that patient has been reached and treatments are then given once or twice a week. Treatments are persisted in for at least six weeks; longer if the Wassermann reaction remains positive. I have often noticed when a patient has developed salivation that his tolerance for the drug after symptoms of salivation have disappeared has increased, and treatment can be resumed where left off without fear of salivation.

If mercury bichloride in normal salt solution is added to blood serum, an albuminate is precipitated which quickly dissolves on shaking and remains in solution indefinitely if the mixture is heated for thirty minutes at 56° C. If an excess of mercury bichloride is added the albuminate precipitates and does not redissolve, except by the addition of more serum or normal salt solution. Precipitation of mercury albuminate takes place if the mercury bichloride in the mixture is in excess of 1 to 300 or gr. 1 in 18 c.c. It may be assumed that these test-tube changes take place when the mercury bichloride solution is injected into the vein, for if some blood is allowed to mix with the bichloride solution in the syringe it will be noticed that the blood is not coagulated, but that a white cloud appears as the serum mixes with the bichloride solution, while the red cells sink to a lower level and remain unchanged. The leukocytes, however, will be found to have been destroyed by the bichloride. This statement is based on microscopic examination.

That mercury bichloride is exceedingly toxic and corrosive is well known, and it could not be used intravenously if it were not instantly converted into a non-corrosive albuminate. That the albuminate is comparatively harmless may be deduced from the fact that it is found in the circulating blood for several days after a single injection. In a case of bichloride poisoning fatal on the tenth day after ingestion, Rosenbloom,[9] of Pittsburgh, found that almost one-third of the mercury recoverable from the body was obtained from the blood alone.

Investigations into the pathology of mercury-poisoning are numerous and exhaustive, but nowhere can one find even an allusion to the pathology, if there is any, that follows therapeutic doses of mercury. The kidney seems to suffer most commonly in mercury-

[9] Am. Jour. Med. Sc., March, 1918, p. 348.

poisoning. I have not so far observed any kidney lesion that could be attributed to the effects of mercury bichloride. In fact, several cases that presented, besides syphilis, mild degrees of nephritis, pyelitis and cystitis, promptly cleared up under intravenous mercury bichloride injections.

The one serious drawback to the intravenous injection of mercury is the frequent occurrence of thrombosis in the injected veins. The condition is not very painful but possesses the potential danger of causing embolism, and may preclude the continuation of the method itself by occluding all the available veins as well as bring the skill of the operator in question. The accident is somewhat less frequent if the mercury bichloride is suspended in serum before injection,[10] but this modification is by no means thrombosis proof. Realizing this to be a serious drawback to the method I must hesitate to advocate its adoption by the profession as a routine practice. But in cases where quick results count for more than the local discomfort and slight chance of embolism would compel us to be cautious this method finds a proper place of application. Some day we may be in possession of a mercurial that is free from these objectionable features and equally as good or better than mercury bichloride in curative value. In that case the intravenous use of mercury will become as universal as that of arsphenamin is today. This is not an inspired prophecy, for experiments have been under way since 1915, conducted by Dr. Schamberg[11] and his coworkers to produce such a mercurial.

[10] The Treatment of Syphilis with Mercurialized Human Serum, Nebraska State Med. Jour., August 19, p. 230. By the Author.

[11] Jour. Am. Med. Assn., May 19, 1917, p. 1458.

REVIEWS

THE NOSE, PARANASAL SINUSES, NASOLACRIMAL PASSAGEWAYS AND OLFACTORY ORGAN IN MAN. By J. PARSONS SCHAEFFER, A.M., M.D., Ph.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy of the Jefferson Medical College of Philadelphia. Pp. 370; 203 illustrations. Philadelphia: P. Blakiston's Son & Co., 1920.

DR. SCHAEFFER describes his book as a "genetic, developmental, and anatomico-physiological consideration," and the work is the outgrowth of extensive studies along these lines conducted at the Yale, Cornell and Jefferson Medical Schools. It is the record of a great amount of work done and should be of much value to the student of anatomy of the special regions indicated in the title. It is, however, purely a scientific treatise on anatomy without any application to surgery, and as such will probably fail to excite the interest of specialists devoted to the practical rather than the theoretical side of medicine. Not that it should be so, for a knowledge of embryology and anatomy should be the invariable basis for all future work in any of the specialties, especially the surgical specialties, although unfortunately this is often overlooked. Neither will the work appeal to the undergraduate student of medicine for the simple reason that his hours, if not his brain, are already too overburdened to make a study such as this seem to him of importance.

As a scientific, painstaking effort this anatomy deserves a great deal of commendation, both on account of the work involved in its preparation, the subject-matter and its admirable arrangement, the great amount of information it contains and the splendid illustrations, most of them original, with which the text is largely interspersed. Many of these are of a distinctly original type, showing sections and dissections of the human fetus and skull made in a unique manner and different from the ordinary text-book presentation of the subject.

General and embryology and development of the skull and special organs comprises the opening chapter, and there is a discussion of congenital defects and so-called anomalies, though Dr. Schaeffer deprecates the use of this term, contending that as there is no fixed type, all organs show some deviation that might be called anomalous. For descriptive purposes, however, the average of the type must be used.

Following this initial chapter the "definitive nose" is thoroughly discussed, and in a most interesting manner. This includes the general nasal architecture, the lateral nasal wall and the septum. Then the various sinuses are taken up in detail, a chapter to each, beginning with the embryology and following the development through childhood to adult life.

But the unusual chapters are those devoted to the nasolacrimal passages—the nasal mucous membrane, the nerve, blood and lymph supply of the nose, and the olfactory apparatus proper.

While much of the subject-matter in these chapters is embryology, and, as such, will be passed over by the average casual student as too deep, or dry, or difficult, the reviewer contends that such should not be the case, and heartily recommends Dr. Schaeffer's book to all students of the head who desire true knowledge of this subject.

G. M. C.

PUBLICATIONS OF CORNELL UNIVERSITY MEDICAL COLLEGE. STUDIES FROM THE DEPARTMENTS OF PATHOLOGY, BACTERIOLOGY AND HYGIENE. New York, 1916–1918, Vol. XVI.

THIS volume embraces a collection of reprints of twenty papers published in various medical journals, five being devoted to researches in bacteriology, five to immunology and ten to histopathology; all are of much interest and value, and are indicative of the research activity of the above-mentioned departments.

J. A. K.

TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION. Vol. XXXVII, illustrated. Philadelphia: Wm. J. Dornan, 1919.

THIS volume contains 34 articles, all dealing with questions in surgery that are occupying the thoughts and efforts of the profession of today. The greater proportion of the contributions is based on the experiences and the knowledge gained from the same in the recent war. As a result of these advantages of experience, many of the obscure and baffling conditions have had developed a greatly improved method of treatment.

Two or more articles on wounds of the knee-joint outline most clearly the most recent advances in treatment, putting it now on a rational, well-understood basis.

The same can be said of wounds of the chest, chronic empyema and thoracic fistula treatment.

Exemplary articles also present surgical problems of reconstruction of peripheral nerve injury, bone transplants, cranioplasty,

fracture of the femur, splenectomy in anemias and many others worthy of mention.

The reviewer has derived much pleasure and instruction from the reading and studying of these transactions. E. L. E.

THE PRINCIPLES OF GYNECOLOGY, A MANUAL FOR STUDENTS AND PRACTITIONERS. By W. BLAIR BELL, B.S., M.D., Gynecological Surgeon, Royal Infirmary, Liverpool. Third edition. Pp. 660; 392 illustrations. New York: William Wood & Co., 1920.

THE appearance of a third edition of this book in less than three years after the second edition is evidence in itself that the work has been well received and is in demand. The present edition has been extensively revised throughout, although the bulk of the book is not greatly increased. Some new illustrations have been added and an improved quality of paper makes the book more attractive. The colored plates presented, although few in number, are unusually good, the coloring being as true to the actual natural color as can be produced. The author retains his arrangement of the subject-matter under pathological headings, and states that, despite objections, it is the only logical way to arrange a book of this kind. It is to be regretted that radium is given such scant attention in the treatment of myopathic bleeding and is not even mentioned in connection with cancer of the uterus. The chapter on electrotherapy has been deleted, but occasional mention of electrical treatments is made in connection with the treatment of various disorders. The misspelling of the word "Fallopian" occurs so generally throughout the book that mention must be made of it. On the whole, the present edition is distinctly more attractive than its predecessors.

F. B. B.

THE AMEBÆ LIVING IN MAN. By CLIFFORD DOBELL, M.A., Assistant Professor of Protistology and Cytology, Imperial College of Science and Technology, London. Pp. 155; 5 plates with 94 figures. New York: William Wood & Co.

THIS latest contributor to our knowledge of amebiasis is a British zoölogist, who during the war had the opportunity of examining thousands of cases of infestation in the British troops. After a brief discussion of methods of fixing and staining the author traces the development of knowledge of amebiasis from the first description in the middle of the last century, through the period of confusion that reigned in the differentiation of parasitic from non-

parasitic forms, to the more accurate information of the present day.

The bulk of the monograph is devoted to E. histolytica and E. coli, the organisms on which his own work was done. He recognizes the now generally accepted harmless role of the latter as well as the frequent occurrence of E. histolytica in patients who have no symptoms of infestation. The organisms are considered exhaustively from the biological viewpoint without going into questions of treatment.

When, however, he comes to the description of the amebæ of the mouth, urine and various organs the author's views run counter to those of many observers in this country. E. gingivalis and, in fact, all amebæ except E. histolytica are regarded as harmless symbions. The bibliography drawn up by the author is extensive, but, unfortunately, in the case of E. gingivalis and less-known amebæ, does not include some of the more important American papers to which he has not had access.

Another peculiarity is the restriction of the generic term endameba to the form described by Leidy as occurring in the cockroach, while a separate genus of entameba is made to include the common man-infesting organisms. M. M. E.

SURGICAL SHOCK. By GEO. W. CRILE, M.D., Professor of Surgery, Western Reserve University, and WILLIAM E. LOWER, M.D., Associate Professor of Genito-urinary Surgery, Western Reserve University. Second edition, thoroughly revised and rewritten. Pp. 272; 75 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

ENRICHED enormously by their experience in the civilian clinic and even more so in the field and base hospitals in France, the authors have rewritten and enlarged their work on anoci-association. As in their first work they present as concisely as possible the principles upon which the doctrine of "anociation," the latest term supplanting that of "anoci-association," is based. All shock theories and their discussion are omitted.

A very long chapter is devoted to the pathology of shock of all kinds, and much that has been taught in the past has been proved true or untrue, as the case may be.

In the chapter on treatment special emphasis is laid upon physiological rest: (morphin) rest liquids, transfusion, nitrous oxide gas anesthesia, local anesthesia or a quick operation.

Morphin is contra-indicated in cyanosis; stimulants are a harm in most instances. Soda solution is next best to blood for transfusion. Solutions other than blood are best given by mouth, bowel or skin in preference to intravenous.

Chapter V outlines in detail anociation technic in general. Later chapters take up each separately, the anociation treatment of specific operative cases, *i. e.*, abdominal operation, appendicitis, gastric surgery, gall-bladder, etc. Separate chapters are devoted to goitre, anociation and blood transfusion.

After many of the chapters is appended a list of "don'ts," which admirably sums up the ideas the authors are striving to drive home.

E. L. E.

REPORT FROM THE PATHOLOGICAL DEPARTMENT AND THE DEPARTMENT OF CLINICAL PSYCHIATRY OF THE CENTRAL INDIANA HOSPITAL FOR THE INSANE, Indianapolis, Indiana, 1915–1917, Vol. VII, pp. 684.

THIS volume summarizes the course of instruction given in nervous and mental diseases and in neuropathology by the faculty of the Indiana University School of Medicine in this hospital, and gives a complete, interesting and valuable summary of the activities of the institution during 1915–1917; 209 pages are devoted to case histories in clinical psychiatry and 423 pages to pathological reports, mainly accounts of necropsy examinations. The volume also contains fifteen papers published by the staff during 1916–1917 and a good index; it reflects great credit upon the institution and its staff, and should prove of much value to those interested in clinical psychiatry, mental pathology and neuropathology.

J. A. K.

HANDBOOK OF SKIN DISEASES. By FREDERICK GARDINER, M.D., B.Sc. (Public Health), F.R.C.S.E., Lecturer on Skin Diseases, University of Edinburgh; Physician for Skin Diseases, Royal Infirmary, Edinburgh. Pp. 160; 46 illustrations. Edinburgh: E. & S. Livingstone. New York: William Wood & Co.

THIS small volume is based chiefly upon the lectures delivered by the author. The views expressed were mostly taught in the Edinburgh School. The subject is treated under fifteen headings and the following classification is employed: Streptococcal and staphylococcal infections; diseases due to animal parasites; seborrhea and the seborrheids: psoriasis; infections of the hairy scalp; urticaria, erythema and allied conditions; bullous eruptions of the skin; dermatitis; diseases due to light, pruriginous eruptions and lichen planus; pityriasis group; tuberculosis and the tuberculides; pigmentary changes and hypertrophies; infective warts, keloids and adenoma sebaceum; neoplasms; syphilis and the syphilides.

The introduction includes the anatomical structure, physiological functions, clinical pathology and the remedial agents used in the treatment of skin diseases. A few selected prescriptions are mentioned in the appendix as of use for the treatment of the common skin affections. The preparations given are largely used in the skin department of the Royal Infirmary, Edinburgh. The volume is compact and readable; naturally in such a small space extreme condensation is necessary and but a cursory review of the subject can be given. If criticism were given the space devoted to some of the rarer diseases might be used with advantage in making additions to the common affections of the skin. F. C. K.

MANUAL OF SURGERY (ROSE AND CARLESS). By ALBERT CARLESS, Emeritus Professor of Surgery to King's College, London. Tenth edition. Pp. 1495; 676 illustrations. New York: William Wood & Company, 1920.

WHEN a text-book of surgery reaches its tenth edition it needs little encouragement from or can be affected only slightly or not at all by the comment of a reviewer. Rose and Carless is becoming to surgery what Gray for many years has been to anatomy, the great English book for medical students. Many others have sought favor and have ceased to appear, but this one remains and renews its contents at suitable intervals. It maintains through the years its text-book form and shows little tendency to become a book of reference. There are no references to the literature, but the editors gave and now Carless alone gives us a condensation and estimate of the value of the best contributions in the literature. Indeed, there is a minimum of mention of the names of individual writers and a maximum of what the editor thinks is the best thought and practice in connection with the various surgical conditions. The war has intervened since the last or ninth edition appeared and the additions to this edition are concerned chiefly with contributions coming from war experience. These have to do largely with the treatment of infected wounds, with compound fractures and with making good the defects of war wounds. Many new illustrations are added. It may now fairly be called a one-man book, so that reduplication is effectively avoided. This permits also what has been accomplished in an eminently successful degree, the absorption of a vast amount of literary material and its expression in a terse, lucid and full discussion of each subject. We have here above everything else a student's text-book, one that lives up to the reputation of the best of its kind. There has been much discussion as to whether this kind of text-book can be of real value to the student. In the reviewer's opinion we have not yet out-

lived the necessity for it, since the best kind of a clinical and demonstrative course on surgery cannot cover the whole field. Let anyone who entertains the opposite view first estimate the number of cases appearing in the best clinical course of which he has knowledge, and then compare these with the subjects covered in a good text-book and see how many conditions have been missed in the clinical course. There will be many times more missed than have been covered. It would be difficult to find any important ordinary surgical condition which has not been disc ıssed in this volume in a manner sufficiently satisfactory for an undergraduate medical student, or, for that matter, most practitioners. Not all surgeons will agree with every statement made and some would like to see reference to war work not taken up, as Duval's brilliant contribution on lung surgery; but when everything else has been said, it will remain a great text-book for students. T. T. T.

COMMON DISEASES OF THE SKIN. By G. GORDON CAMPBELL, B.Sc., M.D., C.M., Lecturer on Dermatology and Pediatrics, McGill University; Phpsician to the Montreal General Hospital. Pp. 229; 177 illustrations. New York: Macmillan Company, 1920.

THE writer has endeavored to provide illustrations and a short description of some of the commoner diseases of the skin, with a few lines on differential diagnosis and methods of treatment. The diseases which have been chosen for the present volume were selected from the statistics of the hospital clinic with which the writer was connected, thereby, possibly, admitting some not properly classed as common because of the large proportion of aliens in his clientèle. In a volume of this size the satisfactory method has been employed of describing the various diseases alphabetically. The dermatological conditions mentioned are as follows: Acne, alopecia, alopecia areata, carcinoma, chloasma, dermatitis medicamentosa, dermatitis repens, dermatitis venenata, eczema, eczema seborrheicum, erythema multiforme, erythema nodosum, favus, furunculus, herpes simplex, herpes zoster, ichthyosis, impetigo contagiosa, keloid, keratosis pilaris, lichen planus, lupus erythematosus, miliaria, miliaria crystallina, milium, nevus, pediculosis, pityriasis rosea, pruritus, psoriasis, purpura, ringworm, scabies, seborrhea, sycosis vulgaris, syphilis, tinea versicolor, tuberculosis, urticaria, verruca, vitiligo.

The author's purpose has been accomplished in providing many and excellent photographs, which serve to illustrate splendidly the diseases of the skin commonly met. The type is large and legible and the paper excellent. F. C. K.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

An Electromyographic Study of Chorea.—COBB (*Bull. John Hopkins Hosp.*, 1919, xxx, 35) finds that choreiform movements give an electromyogram similar to that of a short normal voluntary muscular contraction. Inability to maintain voluntary contraction is clearly shown in the electromyogram. Weakness of muscular contraction is shown electromyographically by lessened electrical discharge.

Electromyographic Studies of Clonus.—COBB (*Bull. Johns Hopkins Hosp.*, 1918, xxix, 247). The studies were made with the string galvanometer for electrocardiographic work. The string used consisted of a gilded quartz fiber 3 micra in diameter with a resistance of 5000 ohms. The author finds that electromyography is a more accurate and more easily applied method for the study of muscular phenomena than those formerly applied to clinical observation. Clonus gives a characteristic electromyogram. Fatigue does not affect the rate of clonus. Increased stimulus increases the rate of clonus and the size of the electromyographic wave but does not change the rate of the active current. The number of active currents per contraction varies with the type of the clonus.

Pericarditis with Effusion and Experimental Studies.—WILLIAMSON (*Arch. Int. Med.*, 1920, xxv, 206). In pericardial effusion the fluid accumulates first along the lower margin of the heart and about the

apex, particularly on the diaphragmatic surface of the heart. With small effusion this is the only place in which fluid accumulates with regularity. The result of the accumulation of the fluid in this position is to push down the left lobe of the liver. This was demonstrable in practically every case, and in many cases it was a very conspicuous feature. Special stress should be laid on this as an early diagnostic sign. The second place in which fluid accumulates is over the great vessel at the base. With small effusion it is occasionally present in sufficient amount to be detected by percussion. With medium-sized effusion this layer is generally thick enough to be demonstrable by percussion and this retrosternal dulness is an important diagnostic sign. With both small and medium-sized exudate we were neither able satisfactorily to demonstrate percussion dulness in the fifth right interspace (Rotth) nor could a rousing of the cardiohepatic (Epstein) angle be made out in a single case. The behavior of the fluid is practically independent of the position of the patient with effusion of the side represented by the injection. In at least 14 of the 33 cases the anterior surface of the heart, in spite of the exudate, remained in part uncovered by the fluid, so that a pericardial friction rub could readily exist. This persistence of the pericardial rub is to be anticipated in cases in which the heart is relatively large, though there is still doubtless space between the vertebral columns at the sternum. From the standpoint of most readily reaching small amounts of fluid the most appropriate sites for puncture are either just outside the apex or in the chondroxiphoid angle.

Stereoroentgenograms of the Injected Lung as an Aid to the Study of the Lung Architecture.—MILLER (*Bull. Johns Hopkins Hosp.*, 1919, xxx, 34). By the use of differential injective masses in the pulmonary arteries and veins the relation of these structures are plainly outlined by stereoroentgenograms. Even though the pulmonary arteries when injected can be recognized, stereoroentgenograms have comparatively dense linear markings along the lateral wall of the bronchi. Under similar conditions the main venous trunk can be made out on the mesial side of the thin bronchus but in its ultimate distribution its branches are not associated with the bronchi. In reading roentgen-ray plates care should be exercised in not mistaking these linear markings for densities produced by pathological changes. Ring-like shadows, with sharp borders that appear along the bronchi, are often due to the plane that the bronchi bear to the observer. When these ring-like shadows are broad, with irregular hazy borders, they are cast by bronchial cartilages. This study suggests once more the importance of a knowledge of lung structure in interpreting densities cast on the roentgen-ray plate. For general directions for the preparation of the differential injection mass which is especially applicable to the study of the distribution of the bloodvessels, see article by MILLER (*Anatomical Record*, 1918, xv, 47). The basis of the injection mass consists of a suspension of cornstarch in 70 per cent. alcohol to which vermilion granules are added. When it is desired to obtain a uniform dense shadow ultramarine blue granules for the less dense and finely granular shadow is desired in the differential injection mass by the use of a greater or less quantity of 70 per cent.

alcohol the injection mass can be made to penetrate to any desired distance within the lungs. If the bronchi alone are to be injected a thick vermilion mass gives the best result, for if the mass is too thin it will penetrate the air sacs and a blurred shadow will result or else the whole lung will appear solid.

Analysis of the Spread of the Excitation Wave in the Human Ventricle.—FAHR (*Arch. Int. Med.*, 1920, xxv, 146) believes the excitation process begins first in the subendocardial layers of the Purkinje system in the neighborhood of the papillary muscle usually a little earlier in the right ventricle and spreads first to the apical layers causing the Q wave. The excitation process is quickly conducted to the basal arborization of the Purkinje system, giving rise to the anacrotic limb of the R. While the excitation process is being propagated through the basal Purkinje system the process in the apical area of the Purkinje system is spreading to the ordinary muscle fibers of the apex. By the time the peak of the R is reached the negativity in the ordinary muscle fibers of the apex is of sufficient magnitude to neutralize the preponderance in the basal Purkinje arborization and cause the catacrotic limb of the R and the ST. The process meanwhile is passing from the basal Purkinje system into the ordinary muscle fibers of the base. Their negativity increases until the effect of the apical fibers is counteracted and the S wave is produced. The negative process begins to die out at the apex, first leaving a preponderance of negativity at the base. This gives rise to the P wave. The form of the electrocardiogram in hearts which have left-sided enlargement is due to the increased length of conducting path in the left ventricle. The right ventricle receives the negativity first. In right-sided enlargement the ventricle receives the negativity first because the path of conduction in the right ventricle is longer. The form of the electrocardiogram in these cases is due to a preponderance of negativity of the left side. The diagnosis of right and left bundle branch lesion as commonly made is probably wrong. In the left bundle branch lesion we should find a high R in lead I and a deep S in lead III. In right bundle branch lesions we get a deep S in lead I and high R in lead III.

Colloidal Gold Reaction and Its Clinical Interpretation.—WARWICK and NIXON (*Arch. Int. Med.*, 1920, xxv, 119). The authors believe that the colloidal gold test is the most delicate of the routine spinal fluid reactions and that with careful technic and proper attention to neutrality the special gold chloride solutions are within the reach of every laboratory worker. They believe that it does not replace any other test but is of independent value. It is of special importance in the early diagnosis of neurosyphilis. The various curves are not specific but of great diagnostic value in connection with other clinical and laboratory findings. A colloidal gold curve may be obtained with or without other positive findings after provocative treatment. The curve does not parallel clinical signs nor give definite evidence of improvement under treatment. Patients with no involvement of the central nervous system or who are non-syphilitic give no colloidal gold curve. Clear-cut

clinical cases of tabes dorsalis may show all the spinal fluid reactions negative both before and after treatment. A curve in zone 3 with a negative cell count and negative or faintly positive globulin is strongly suggestive of a brain or cord tumor or myelitis. Curves in zones 1 and 2 may be found in non-syphilitic conditions such as multiple sclerosis and brain abscess. A cell count above five the authors regard as pathological, but the cell count is of no value in indicating duration or severity of the process or improvement. The colloidal gold reaction should be included in every spinal fluid analysis and neurological examinations as well as in all cases of general syphilis.

A Clinical Study of Yellow Fever.—ELLIOTT (*Arch. Int. Med.*, 1920, xxv, 174), from a clinical and pathological study of about seventy cases of yellow fever observed in Guayaquil, Ecuador, during the summer of 1918, considers clinically yellow fever is similar to infectious jaundice. The differences existing between the two diseases appear to be chiefly those of degree. There is more marked jaundice and less hemorrhage in yellow fever than in infectious jaundice. Although the hemorrhage is a usual occurrence in all severe cases, yellow fever is not a true hemorrhagic disease. The hemorrhage apparently follows necrosis of parenchymatous tissues and endothelial cells. The jaundice of yellow fever appears to be a non-toxic, dissociated, hepatic (suppression) type. Death appears to be due to uremia. It is usually preceded by anuria. There is an intense degeneration of the epithelium of the convoluted tubules. The glomeruli and collecting tubes remain relatively free from degeneration. Convalescence in all patients who survive is prompt. The complete restitution of all organs to normal is remarkable. No evidences of impaired liver or kidney function remain, although intense parenchymatous changes must have occurred.

Fluoroscopy of the Cerebral Ventricles.—DANDY (*Bull. Johns Hopkins Hosp.*, 1919, xxx, 29) has previously shown that if air is substituted for the cerebrospinal fluid in the ventricles of the brain an accurate outline of the lateral ventricles can be cast in a roentgenogram. In this communication the author shows that the lateral ventricle when filled with air can be clearly seen under the fluoroscope. Twenty-five cases have been studied by this method. The results in adults are just as good as in children. By fluoroscopy hydrocephalus can be accurately diagnosed at all stages of its development. Several unsuspected cases of hydrocephalus have been demonstrated by the fluoroscope. The diagnosis of a false ventricular hernia (ventriculocele) was made with certainty because the air from the ventricle could be seen to pass directly into the swelling. Fluoroscopy of the ventricle has practically the same range of utility as ventriculography, and almost the same results have been obtained. Following the injection of air in the ventricle both fluoroscopy and ventriculography should be used.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK,

AND

CHARLES C. LIEB, M.D.,

ASSISTANT PROFESSOR OF PHARMACOLOGY, COLUMBIA UNIVERSITY, NEW YORK.

Tubing as a Cause of Reaction to Intravenous Injection, Especially of Arsphenamin.—From a study of the "tubing reaction" following the administration of arsphenamin through new tubing, STOKES and BUSMAN (*Jour. Am. Med. Assn.*, 1920, lxxiv, 1013) conclude that "A certain widely distributed brand of so-called pure gum rubber tubing seems to contain, when new, a toxic agent responsible for a definite type of reaction following the intravenous administration of arsphenamin, and possibly also of alkaline solutions and transfusion mediums." The toxic substance gradually disappears from the tubing on use. It is not destroyed by the ordinary sterilization by boiling, is insoluble in water, appears in toxic amounts in arsphenamin, dilute NaOH solutions, etc., merely by passing them through a new tube en route from container to vein, and is not apparently associated with the mechanically removable debris from the inner surface of the tube. The toxic substance is apparently removable in the first instance by soaking the tubing for six hours in normal NaOH solution and rinsing. The reaction induced by this toxic agent consists of chills coming on from thirty to sixty minutes after injection, with nausea, vomiting, diarrhea, a sharp rise in temperature, headache, lumbar cramps, etc. The reaction was induced by the authors in typical form in dogs.

Treatment of Leukemia with Deep Roentgenotherapy.—ROSENTHAL (*Berl. klin. Wchnschr.*, 1919, lvi, 1113, abstracted in the *Journal of American Medical Association*, April 17, 1920) reports striking results in the treatment of leukemia with deep roentgenotherapy. In addition to the reduction in the number of leukocytes and diminution in the size of the spleen, the chief value lies in the disappearance of the subjective symptoms in cases in which other therapeutic methods had failed. He gives in detail the history of a case that has been observed now for three years in which after several treatments distinct improvement occurred. For five or six months after each treatment the patient felt well and was able to work, then there was a recurrence of symptoms promptly relieved by a new treatment. He considers that the roentgen ray is the most reliable treatment in leukemia. Severe reactions, however, do occur. He recommends that the treatment be intermittent.

Administration of Arsphenamin by Retention Enema.—MANDRACCHIA (*Med. Record*, 1920, xcvii, 144) advocates the administration of arsphenamin by the retention enema method. In the gynecological section of

the Metropolitan Hospital this method has been employed in 25 cases representing the various stages of syphilis. Twenty per cent. of these cases have been completely cured serologically and clinically; 36 per cent. have improved clinically and the Wassermann reactions changed from four plus to two plus. In 40 per cent. the Wassermann reaction was unaffected but the patients showed marked clinical improvement. When these arsphenamin enemas were first started there was some apprehension as to possible local injury to the alimentary tract. About 500 of these enemas have now been given with no apparent injury. Mandracchia believes that the drug undergoes some chemical change in the intestinal tract. He concludes that there are no contra-indications to this method of administration and that the slow absorption is an advantage in preventing the production of nitroid crises. For the technic of the enema method of administering arsphenamin, the reader must consult the original article.

Inhalation Treatment in Pulmonary Tuberculosis.—Robinson (*Med. Record*, 1920, xcvii, 143) believes that creosote is the only drug which, when properly used, is of real value in the cure of pulmonary tuberculosis. He generally uses a mixture of equal parts of beechwood creosotes spirit of chloroform and alcohol. Ten to twenty drops of this are poured upon the moistened sponge of a perforated zinc inhaler. With practice the patient can wear this inhaler almost constantly with little or no discomfort, the drops on the sponge being renewed whenever the odor of creosote becomes less appreciable. If creosote is given by mouth it should be in small, repeated doses. Given undissolved in capsules it is often upsetting to the stomach. During any treatment with creosote it is necessary to examine the urine every day or two; if albumin appears the length of time or the frequency of use must be lessened.

Experience with the Schick Test and Toxin-antitoxin and a Plea for Their Use in the Extinction of Diphtheria.—Lilly (*Boston Med. and Surg. Jour.*, 1920, clxxxii, 110) has drawn the following conclusions from his experiences with the Shick test and the toxin antitoxin immunization of children susceptible to diphtheria. He believes that in institutions, schools or communities where diphtheria has been prevalent for a considerable period of time the universal taking of cultures is practically useless. A non-virulent bacillus is often found to be persistent in the throats of so-called chronic diphtheria carriers. He believes that repeated passive immunization does not protect and that such immunization lasts less than three weeks. He found that toxin-antitoxin does give absolute and persistent immunity to diphtheria when more than one month has elapsed after its administration. Reactions are much less frequent and severe. On the other hand, toxin-antitoxin has no curative properties and does not immediately protect against diphtheria. He is also of the opinion that the Schick test is not rapid enough to be of immediate use in cases exposed to clinical diphtheria and should be used only to separate immunes from non-immunes. The active immunization of non-immunes should be used to protect susceptibles when there is no immediate necessity to protect life. He believes that in the general use of the active immunization of non-immunes we have a means of exterminating diphtheria.

Mercuric Chloride Poisoning from Vaginal Injections: Two Fatal.—BLAND (*Jour. Am. Med. Assn.*, 1920, lxxiv, 1227) gives details of three cases of mercuric chloride poisoning following the vaginal injection of strong solutions for the prevention of conception or the induction to abortion. Two patients died, the fatal outcome being due to complete suppression of urine. In each case there was a violent local reaction for which local agents had been applied without relief. Details of the history and course of illness of each case are given, with blood analyses, etc. The treatment is not detailed. In the same issue of the *Journal* (p. 1230), De Porte gives the case of a woman who died from acute traumatic nephritis about twenty-four hours after the insertion of two 7.3 grain mercuric chloride tablets into the vagina to prevent conception.

A Comparison of Methods for Determining Thyrotoxicosis.—From observations on a selected group of 11 cases, WOODBURY (*Jour. Am. Med. Assn.*, 1920, lxxiv, 997) concludes that complete methods of examination with special attention to the possibility of errors in case of psychoneurotic patients should furnish the basis for diagnosis, rather than reliance on any functional test, though these tests are of great value in the compilation of evidence, especially in relation to the degree of toxicity. He found the epinephrin chloride test clear, positive, and of moderate degree in 6 cases; clear, positive, and of more marked degree in 5. Basal metabolism results in the 11 cases were: 11 per cent. high; 6 per cent. low; 5 per cent. high; 8 per cent. high; 8 per cent. high; 20 per cent. low; 4.5 per cent. low; 14 per cent. low; 2 per cent. high; 7 per cent. high; and one, flat normal. Readings not varying more than 15 per cent. from the normal were regarded as normal. On section, the eleven thyroids all showed definite abnormalities of a type suggesting functional overactivity.

Meningitis Treated by Intrathecal Injections of the Patient's Blood Serum.—The clinical features and the character of the cerebrospinal fluid in the case reported by WATERHOUSE (*British Med. Jour.*, January 10, 1920, p. 45) were typical of cerebrospinal fever, although the meningococcus was absent from the spinal fluid. The fact that the examination was not made until the eighth day of the disease probably accounts for their absence. On admission the patient appeared desperately ill and the next two days the symptoms increased in severity. It was therefore decided to try the effect of intrathecal injections of the patient's own blood serum. Five injections were given in all. Improvement set in from the time of the first injection and recovery was rapid and complete. Helmitol (at first 10 grains every four hours until hematuria appeared, when the dose was reduced by half) was also given, but the author attributes the recovery of an apparently hopeless case to the intrathecal injections of serum.

Studies on Experimental Pneumonia. IV. Results of Prophylactic Vaccination Against Pneumococcus Pneumonia in Monkeys.—CECIL and BLAKE (*Jour. Exp. Med.*, 1920, xxxi, 519) found that subcutaneous inoculation of monkeys with pneumococcus Type I vaccine in doses

comparable with those employed in man did not protect them against pneumonia from either Type I or Type IV pneumococcus. However, invasion of the blood stream by pneumococcus in vaccinated animals was usually slight and the proportion of recoveries considerably higher. Pneumococcus saline vaccine, while failing to protect the animal against pneumonia, produced a greater amount of protective substance in the serum than did pneumococcus lipovaccine, and is probably a better antigen. The vaccination gave definite protection against experimental pneumococcus septicemia; thus, vaccination may induce a humoral immunity without protecting against intratracheal infection. A strict analogy cannot be drawn between pneumococcus immunity in monkeys and in man, since in the latter a considerable amount of resistance already exists, while monkeys are highly susceptible to pneumococcus infection.

Protective Inoculation Against Influenza. — WYNN (*British Med. Jour.*, February 21, 1920, p. 254) advocates the use of a vaccine containing equal numbers of Pfeiffer's bacilli and various strains of pneumococcus and streptococcus recently isolated. With pneumococcus only first cultures are used, with streptococci either primary or first subcultures. He gives two doses, 200 million and after one week 400 million. During the epidemic period of 1918–19, of 680 persons injected only 14 developed influenza, and 4 of these were attacked three months after the last injection. In all cases the disease was mild and there was no pneumonia. Wynn reviews at some length results obtained from protective inoculation by both British and American observers.

The Therapeutic Value of Oxygen in Pulmonary Lesions: Preliminary Note.—Observations on two cases of pneumonia, one of bronchitis, and on a normal individual, led MEAKINS (*British Med. Jour.*, March 5, 1920, p. 324) to conclude that in certain respiratory diseases when there is anoxemia of the arterial blood the administration of oxygen will diminish this anoxemia and so relieve the cyanosis. If the oxygen be given in sufficient concentration in the inspired air the arterial saturation with oxygen may be raised above normal in both normal individuals and those suffering from respiratory diseases. The method of administration was that devised by Haldane.

Severe Mercurial Stomatitis Caused by the Administration of Calomel.—GORDIN (*Jour. Am. Med. Assn.*, 1920, lxxiv, 1163) reports two severe cases of mercurial stomatitis following the use of calomel as a cathartic: an acute case, in which the patient died on the seventeenth day after the ingestion of 2 grains of calomel and a case of thirteen years' standing showing the results after recovery. In addition to these 2 severe cases a number of milder cases of salivation have been seen by the writer. It is definitely known that the action of calomel as a cathartic is simply a mechanical irritation, due to the metallic mercury liberated, and that it has no action on the liver. He concludes that there are many efficient cathartics which are less dangerous than calomel.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

The Influence of Food upon Development.—VAN DER BOGERT (*Arch. Ped.*, December, 1919) asserts that to suggest that diet is the sole or all-important factor in the prevention of disease is to court criticism as a faddist, but he speaks from an experience of twenty years, ten of which have been devoted to the treatment of children, which has convinced him that rational feeding in infancy and childhood has a real bearing upon the development of mental and physical strength in the adult and in the resistance to infection. Experience seems to show that the present-day civilized woman cannot produce a satisfactory milk for longer than one year. Babies kept longer at the breast usually develop less well, and do better when other foods, properly prepared and administered, are given. Physical defects and digestive disorders are frequent in the later life of children who give a history of having been long nursed at the breast. The real danger of prolonged nursing lies in the likelihood of overfeeding, since it practically always means breast milk in addition to other foods and much of the nursing is practiced at nights when the digestive organs should be at rest. The young carnivora remain with the mother for a period of a few weeks to even more than a year. Before they are weaned they begin to scrape off the meat from the prey that the mother brings home, and so gradually acquire a taste for their future food and an ability to digest it. This argues for gradual weaning, a gradual accustoming of the digestive organs to their future task, the early administering of green vegetable juices, fruit juice and beef juice. Prolonged bottle feeding frequently hinders development. The question of milk as a food in later childhood is of importance to be considered. Owing to certain propaganda as to the value of milk as a food, too much of it is being given to older children to the exclusion of other foods, or in addition to other foods. He advises small quantities of milk but a mixed diet of preferably three meals a day. Older children to develop normally must have digestive rest. At eighteen months he recommends three meals. There should be sufficient interval to insure digestion and a period of rest. He recommends a somewhat similar procedure in infants also; in the early months feeding every three hours, every four hours after six months and with longer periods at night.

Anatomical Considerations in the Rectal Prolapse of Infants.—TODD (*Ann. Surg.*, February, 1920) places rectal prolapse in three types as follows: At the anal margin; at a certain distance above the anal margin and protruding; at a higher level (pelvic colon) and not protruding. The second and third of these types clearly belong to the class of intussusception, differing from the ordinary clinical condition only in that the entering portion of bowel commences its progress through

the intussusception low down in the distal colon or in the rectum. There are two locations favorable for the development of an intussusception, namely, the pelvirectal junction, and the subdivision of the rectum at the great valve of Houston. At both of these areas there is a more or less marked infolding of the bowel wall, and both correspond to the junction of a higher and comparatively mobile portion to a lower and more fixed portion. As regards the causes of rectal prolapse, especially of that type beginning at the anal margin, given in the literature, mention must be made of overloaded rectum, straining at stool, lack of muscular tone in the pelvic diaphragm, and diminution of fat in the ischiorectal fossæ in rickets and wasting diseases. Another factor is the fact that in infants the rectum is more vertically placed in the pelvis than in the adult, because of the more vertical position of the sacrum. From a study of anatomical material he finds that, estimated by the position of the great valve of Houston, the rectum at birth presents practically the same relation to the vertebral column as in the adult; that the rectal stalks are of the same proportionate lengths and therefore there is no greater laxity; that the only anatomical character which can be of importance in infantile prolapse are the comparative straight sacrum and the consequent more vertical rectum.

Is Fat Starvation a Causal Factor in the Production of Rickets?—HUTCHISON (*Glasgow Med. Jour.*, January, 1920) says that there are two main lines of thought regarding the primary etiological factors in the causation of rickets. One follows the assumption that it is a disease akin to beriberi and scurvy, and is due to a deficiency in the diet of the fat soluble growth-producing factor. The other thought is that it is not a deficiency disease, but that it is caused by lack of exercise and want of fresh air during the period of development. Paton and Findlay believe that while the amounts of fat in the diets of non-rachitic families is on an average 10.7 per cent. higher than that of the rachitic, the overlap is so great that a defective supply of fat cannot be considered as playing an essential part in the causing of rickets. The author made a series of studies to determine that although the supply of fat is adequate the rachitic may not be able to absorb what is ingested, and that fat starvation is really present. He made three tests as follows: (1) To determine if there is an excessive loss of fat through pancreatic insufficiency; (2) to determine if there is an excessive loss of fat through the passage of unduly large movements; (3) to determine if there is any true defective absorption of fat. The first test showed there was no evidence of defective digestion of fat and therefore no defective absorption of fat from this cause. The second test showed there was no excessive loss of fat due to large stools. The third test showed there was no falling off in the absorption of fat, but it was shown that the more fat that was given the more the rachitic child would absorb. He was unable to show that calcium deficiency was brought about by defective fat assimilation.

Acute Cholecystitis in Children as a Complication of Typhoid Fever.—REID and MONTGOMERY (*Bull. Johns Hopkins Hospital*, January, 1920) have collected 18 cases of typhoid fever in children under the age of fifteen who either died or were operated on for complications arising

in the gall-bladder. In 1 case the acute cholecystitis did not develop until eight months after recovery from this disease. In all the other cases the complication came on during the course of the disease. Eight patients died without surgical treatment. All of these cases occurred prior to 1893. Since that time 10 cases have been treated surgically. One of these died, making a mortality of 10 per cent. The records of the earliest were not supported by any bacteriological studies. In recent years cultures of the gall-bladder have usually been made at the time of operation. In this connection the leukocyte count is of interest. When cultures have shown a pure culture of typhoid bacilli, the count has usually been relatively low, usually about 10,000. In one case in which cultures were not made there was a leukocyte count of 33,000, and in another which showed an organism not definitely identified, there was a count of 21,000. Thomas in 1901 collected from the literature 154 cases of typhoid fever complicated by cholecystitis. Perforation of the gall-bladder occurred in 39 of these. Twenty-eight were not operated; 11 were treated surgically with a mortality of 54.6 per cent. In 1908 Ashhurst collected 21 cases of acute cholecystitis in which an operation was performed during the course of typhoid fever. Eight recovered. Price in 1916 collected 8 other operative cases, and added 1 of his own, bringing the total of cases to 30 cases. In the 9 collected cases of Price, there was 1 death and this was due to intestinal perforation, two weeks after the operation on the gall-bladder. The 6 cases reported in this paper all recovered.

Some Facts and Fallacies of Maternal Feeding of Infants.—Love (*Southern Med. Jour.*) says that the gross appearance of breast-milk furnishes an unreliable index as to its suitability for the baby. Before pronouncing milk as being too rich in quality, the presence or absence of colostrum bodies should be determined by microscopical examination. The mere fact that milk is scant in quantity also furnishes no valid excuse for the withdrawing of the infant from the breast, but rather calls for supplemental feedings. Conclusions drawn from examinations of milk chemically are liable to be misleading. The laboratory findings should confirm clinical observation. In influencing the quality of breast milk the maternal dietary, while of some importance, is a smaller factor than causes which operate through the medium of the mother's nervous system.

Infant and Child Mortality.—Schwarz (*Am. Jour. Dis. Children*, April, 1920) presents important statistics in this paper. The material was taken from the social histories of 10,000 families covering a period of ten years. These families were of heterogeneous nationalities, and their social status was that of the so-called working element. Because of the great amount of work involved and because of the economic situation of the world rendered this an opportune time for the presentation of this study only about 7000 histories were analyzed. In 6968 families there were 27,711 pregnancies including miscarriages and stillbirths, an average of 3.9 per family. Of these 27,711 pregnancies 2239 were miscarriages and 413 were stillbirths, the remainder, 25,059 represented the number of living births, or 3.6 live-born children to each family. The total number of deaths under one year of age of living births was

3232. From the first to the eighth year there were 1081 additional deaths, or a total of 4313 deaths of living births. Including miscarriages and stillbirths the total number of deaths up to eight years was 6965 in the 27,711 pregnancies or 25 per cent. Computed in terms of per thousand pregnancies the miscarriage rate was 80.7 per thousand, and of all living births was 89.3 per thousand. The infant death-rate up to one year of age was 128 per thousand living births. In contrast it is of interest to note that the death-rate in the same age group was 70 per thousand of the children who were under the care of the clinic. The child death-rate (up to eight years) reached 172 per thousand.

Acute General Peritonitis in Infants.—Boss (*Pennsylvania State Med. Jour.*, March, 1920) reports four cases, two of which were males and two were females. The ages were four weeks, eight weeks, three weeks and four months respectively. Only one case was characterized by persistent vomiting. Neither diarrhea nor constipation were prominent features. All had some elevation of temperature, which was high at the onset. Cyanosis was present in one case and great depression was present in all. The symptom common to all was marked distention of the abdomen with general abdominal tenderness. In all four the peritonitis seemed to be a part of a general septicemia complicating infectious processes elsewhere in the body.

Studies with a New Method of Determining the Coagulation Time of the Blood in the Newborn.—Rodda (*Am. Jour. Dis. Children*, April, 1920) describes a method in which the apparatus consists of a spring lancet or scalpel, two one and a half inch watch-glasses and a No. 6 lead shot. The first step consists of cleansing the glasses and shot with soap and water followed by alcohol and ether. The lance should be sterile. The finger of the infant is sponged with ether, and a puncture is made to produce free flow of blood without pressure. A clean watch-glass containing a No. 6 shot receives the second drop of blood. The second watch-glass is inverted over the first. They are tilted every thirty seconds until the shot no longer rolls, but is firmly imbedded in the clot. The time is reckoned from the falling of the first drop until the shot is firmly fixed in the clot. Determinations are made to the nearest half minute. This method has the advantage of being simple, easily applied in the newborn, and gives results more accurate than those obtained with the Lee and White method. The average coagulation time in the newborn with this method is seven minutes, with a normal average of between five and nine or ten minutes. The average bleeding time in the newborn with Duke's method is three and a half minutes with a normal range of from two to five minutes. In the normal newborn there is found a tendency to prolongation of these times in the first days of life. Hemorrhage is accompanied in many cases with an exaggeration of the tendency or markedly prolonged coagulation and bleeding time. The coagulation and bleeding time should be studied in conjunction. Routine determination in the newborn will allow the selection of at least certain of the hemorrhagic conditions before the onset of symptoms, and give the indication for the administration of blood. The method will allow for a check on blood therapy in hemorrhages of the newborn.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Retention of Urea in Disease of the Kidney.—SCHIOTZ (*Norsk Magazin*, April, 1919, No. 4) describes three cases of detachment of the retina in pregnant women who had nephritis. Each patient was a primipara, one seventeen, one twenty-nine and one thirty-five years old. Each had albuminuria and eclampsia, but without marked edemia. They were all emmetrope and detachment of the retina occurred after several convulsions, in the older woman in both eyes. In this case, the accident happened at the seventh month and persisted for a month after the patient had premature labor. The retina finally returned to its place, with considerable division. In this woman, during a second pregnancy, albuminuria returned five years later; but disappeared at spontaneous premature labor, at seven months. At this time, vision was not affected. In the second patient, there was retinitis and detachment of the retina, which lasted until delivery, at seven months, in all about two weeks. Finally, the retina returned to its place, and in two days, there was no trace of the detachment. The younger of the three patients developed eclampsia, after full-term delivery, and detachment of the retina occurred, without any signs of retinitis. In this woman, the detachment has persisted for a year. The fourth was that of a myopic woman, in her fourth pregnancy, who had detachment of the retina. The affected eye became totally blind and, in the other, detachment of the retina occurred just before term, in the fifth pregnancy. There was no trace of sugar or albumin in the urine. Operation was done on the eye just before delivery and, within a week, the retina had returned to place but vision was much affected, and grew worse after a few months. The writer knows of only four similar cases of detachment of the retina in pregnant women, without albumin in the urine, and of the five total cases, three were strongly myopic. The detachment persisted unmodified in all but one case. In two of the others, the retina in the other eye became detached at the fourth or the sixth month, in a later pregnancy. In both cases, artificial delivery at once was followed by restoration to place of the retina and the gaining of vision. It is clearly shown that the longer the time between the detachment of the retina and the delivery of the child, the smaller is the chance of the retina going back to place. Accordingly, when this accident happens, pregnancy should be terminated at the earliest possible moment.

Coexistent Disease of the Appendix and Pelvic Organs in the Female.—CHILD (*Am. Jour. Obst.*, July, 1919) studied the relation between disease of the appendix and pelvic disease in the female in 748 operative cases. In 746 the appendix was removed 339 times, it was physiological 244 times, a percentage of 32.57 for the whole series. When there was

an inflammatory condition of the tubes or ovaries the average was 46.70 per cent., if the inflammation was limited to the right broad ligament 66.66 per cent. had involvement of the appendix, and when the inflammation was on the left side or the uterus but 18.42 per cent. of cases had disease of the appendix. When both tubes and ovaries were involved, 38.38 per cent. In all cases of inflammation of the right tube or ovary the appendix was involved 43.95 per cent. and appendix actually adherent to the adnexa on the right side in 19.09 per cent. Among these cases there were 99 in which the appendix was removed at the request of the patient but microscopic examination failed to find disease. There was marked atrophy of the appendix in 10 cases and then it was not removed. The appendix was found in the pelvis adherent to a diseased right tube or ovary in 75 cases in which 25 showed acute inflammatory changes while 37 were subacute or chronic. One of the most interesting cases in the whole series was that of right tubal ovarian abscess with adherent appendix, where the lumen of the appendix connected directly with the abscessed cavity. The infection in this case was by the colon bacillus. In another patient the pyosalpinx had ruptured spontaneously through the abdominal wall, a sinus thus made communicated with the uterine cavity through the tube and the patient menstruated regularly each month through this sinus. At operation a chronically inflamed appendix four inches long was found also adherent to the abdominal wall and fused to the tube by dense adhesions. A cystic appendix filled with gelatinous material and measuring 6.5 cm. in length was found in 1 case. The author concludes that disease of the pelvic organs in the female is an important exciting cause of appendicitis and that to a lesser extent inflammation of the appendix may cause disease in the right Fallopian tube. He believes that the primary source of infection is more often in the pelvic organs than in the appendix. When this inflammation is on the right side of the pelvis, the appendix is involved four times more frequently than when on the left. It follows that when operating one should always remember that both pelvic organs and appendix should be inspected. The appendix should be removed if possible whenever the abdomen is opened. The author goes to the extent of saying that appendicitis in the female is associated so frequently with pelvic disease that it should be considered a gynecological condition. Obstetricians are interested directly in inflammation of the appendix as it frequently complicates pregnancy and the puerperal state. It is not, however, a frequent complication of puerperal septic infection and hence if the statements of the author quoted are correct, non-puerperal inflammation of the pelvic organs must be the most frequent cause of appendicitis in the female. The circumstances in pregnancy are peculiarly favorable for the development of the colon bacillus and such has most usually been found to be the cause.

Report of a Case of Full Term Ectopic Pregnancy.—Rawls (*Am. Jour. Obst.*, July, 1919) reports the case of a primipara, aged nineteen years, seen in the twenty-second week of her pregnancy. At six weeks a catheter or sound had been introduced, which caused bleeding for several days; it was thought that abortion had been accomplished until a few days before coming to hospital, when the patient's abdomen suddenly enlarged. On admission the fundus was above the umbilicus,

a placental bruit could be distinctly heard and it was thought pregnancy was further advanced than the history indicated. The patient then passed from observation until five months later. She had been well until the previous week, when she was attacked with pain over the gall-bladder, with nausea, vomiting, constipation and voiding small quantities of highly colored urine. The patient was slightly jaundiced and was treated by catharsis, diet and colon irrigation without improvement. When admitted to hospital temperature was 101°, pulse 144 (weak and irregular), respiration 30 and difficult. On palpation a firm tumor mass could be felt extending from upper left quadrant to the umbilicus. There was well marked dulness in the flank on the left side, just below the umbilicus could be heard a fetal heart and below this the placental bruit. On vaginal examination the cervix was displaced to the left, the external os admitted finger only to the internal os, behind the cervix was a cystic mass with indefinite firmer mass above on the right and below the level of the internal os. There was there a small hard mass which suggested some part of the child. The patient was thought to be at full term with natural intra-uterine pregnancy complicated by toxemia, with either incomplete rupture of the uterus or an ovarian cyst with twisted pedicle. The patient improved after admission to the hospital, but the fetal heart sounds ceased and no fetal movements were observed. The patient continued to improve, the urine grew better, blood analysis showed carbon dioxide in the blood 23 with marked reduction in urea. On the sixth day after admission abdominal section was performed, there was considerable vaginal bleeding from preparation and examination and the vagina was packed with gauze. A sound was not passed into the uterus. When the peritoneum was opened there was a gush of bloody serum. The fetus was found with head toward the left of the sternum showing distinctly through a thin sac, this sac was thicker posteriorly and adherent at intervals to the omentum, large intestines and peritoneum. The pedicle was in the region of the left broad ligament. The membrane was then opened and amniotic fluid and child removed. On separating the adhesions the pedicle was at the site of the left tube and the upper part of the broad ligament above the ovary and extended to the uterine horn but did not involve the fundus of the uterus. The pedicle was firmly secured and the placenta and membrane removed with very little loss of blood. The uterus was the size of a four months pregnancy and had been carried backward, upward and to the left. The pedicle was secured with ligatures and sutures and portions of the membrane were removed from the omentum, intestines and peritoneum, the abdomen was closed without drain. The patient made an uneventful recovery and was convalescent in two weeks. The child was at term and macerated.

Labor Complicated by Breech Presentation with Fetus in Hyperextension.—LAFFONT (*Arch. mens. d'obst. et de gyn.*, February, 1919) reports the case of a primipara, aged thirty years, admitted to the hospital in labor with breech presentation. The membranes ruptured spontaneously and a large quantity of amniotic liquid escaped. When dilatation was complete a foot of the child appeared at the vulva, the head descended into the pelvic excavation and about half hour afterward a male child, weighing 2780 gm. was born in a condition of appar-

ent death. The child was finally resusciated but breathed very badly. It was found in a condition of hyperextension and this is well illustrated by a photograph of the infant. An autopsy was performed and the spinal cord of the child exposed, from the border of the seventh cervical vertebra to the first dorsal vertebra the spinal cord was bare, the meninges terminated in the skin at a point where the roots of the seventh pair of cervical, down to the eighth pair of cervical nerves had issued from the cord. The seventh pair of cervical nerves was denuded, deprived of its envelope of membrane and the left branch was disintegrated. The eighth pair was not denuded but one observed that this nerve proceeded obliquely. On opening the membrane of the cord it was found that there had been a hemorrhage into the arachnoidean space. This extravasation of blood or hemorrhage had great effect through its pressure upon the functions of the cord. The rupture of the membranes of the cord had evidently been caused by condition of hyperextension of the head upon the trunk during the course of fetal development. Examination by roentgen ray failed to find any bony lesions. The Wassermann reaction in the mother was negative. The author quotes Bar's case, in which the cranium was markedly dolichocephalic.

Influenza and Pregnancy and the Puerperal Period.—CALDERON (*Jour. Am. Med. Assn.*, September 27, 1919) reports 36 cases of influenza in parturient women of which 9 occurred in the puerperal period. It was found that among pregnancy patients, independently of bronchopneumonia or lobar pneumonia, that influenza exerted a very pernicious influence. In patients who were not pregnant it caused menstruation to appear at unnatural periods. The great element of mortality in these cases was lobar pneumonia during pregnancy, while in the puerperal period bronchopneumonia was the cause of death. Among the infants there were seven deaths, including intra-uterine deaths and there was 1 case in which the temperature of the newborn child rose very high.

Interstitial Pregnancy.—VAUDESCAL (*Arch. mens. de obst. et de gynec.*, April, 1919) described a remarkable case of interstitial pregnancy which continued for more than four months without serious accidents from pressure. The placenta in the original implantation cavity of the ovum continued to develop, while the fetus was encysted. In this and another similar case the operation consisted in removing the uterus. In the third case an emergency section was done for hemorrhage and a wedge-shaped reaction was performed. From a study of this and other cases we may conclude that interstitial pregnancy develops like other ectopic gestation and also ruptures in a similar way. In diagnosis the lack of symmetry in the adnexa is significant and also the fact that on the affected side the round ligament is inserted at the site of the tumor. Tubal pregnancies are usually found more posterior toward Douglas' cul-de-sac. Where the ectopic gestation is anterior the development of the case will usually make the diagnosis clear. It must not be forgotten that the ovum sometimes passes into the uterine cavity when it has originally been located in the angle of the uterus. If, however, it is a genuine interstitial pregnancy it proceeds to rupture. Although careful search was made there was no evidence that decidua were produced in these cases.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

ASSISTANT INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Treatment of Uterine Cancer.—TAYLOR (*New York State Jour. Med.*, 1920, xx, 8) very properly divides the treatment of uterine cancer into four parts, namely, publicity and education, prophylaxis, treatment of operable cases and treatment of inoperable cases. The importance of publicity, education and prophylaxis needs no further discussion in a brief abstract of this kind, therefore we shall confine our attention to his views on the treatment of cancer after the diagnosis has been made. Our definition of an operable case is frequently changed. A few years ago, before radium was in common use, many cases were considered operable that would now be placed in the inoperable class. Formerly, we knew that if a case was not operated upon there was no hope; therefore, we were led to operate on many cases in which the chance of cure was comparatively small and the risk of the operation correspondingly great. With the use of radium, however, the case is not necessarily hopeless without operation, and even if not permanently cured, life can be prolonged and the patient given great comfort by its use. The use of radium, however, has developed another class of cases, that is, the cases which were inoperable before treatment, but as the result of the use of radium become operable. In the treatment of operable cases, that is, cases in which the growth is limited to the uterus, with possibly a limited superficial involvement of the vaginal walls, Taylor believes that a combination of radium and operation offers the greatest hope of a permanent cure. It is his custom in such cases to make an application of radium, usually 100 mg. for twenty-four hours, and then after a few days, usually less than a week, to allow the possible reaction from the radium to subside, to do such abdominal hysterectomy as the case indicates. If the case is favorable he does a radical abdominal hysterectomy, with the isolation of the ureters and the removal of the pelvic connective tissue as far as possible. If the case is more difficult on account of a thick abdominal wall or any concurrent constitutional disease he would be satisfied with a simple hysterectomy. It has been stated that a hysterectomy after the use of radium is associated with greater difficulty on account of increased liability to hemorrhage and to the absence of the usual planes of cleavage. It has not been Taylor's experience that the increased difficulty has been sufficient to contra-indicate an operation following the use of radium; there may be some increased bleeding, but in no case has this been difficult to control. There is usually some edema about the bladder fold and at the bases of the

broad ligaments, but this has never interfered materially with the operation nor with the subsequent healing of the wound in any of his cases. Following the operation, and previous to the patient's discharge from the hospital, that is, at the end of three or four weeks, an application of radium to the top of the vagina is made. There are, of course, cases which are so far advanced that it would be folly to do anything other than to use morphin for the relief of pain and discomfort and proper douches for cleanliness. In these cases the possibility of causing irritation to the bladder or rectum, associated with additional discomfort, is such that the cases are more comfortable without any local applications of radium. Excluding these advanced hopeless cases, there has been nothing in Taylor's experience in the treatment of inoperable cancer of the cervix that has approached the use of radium in its results. It has advantages over the use of the cautery in that it can be applied without an anesthetic, with practically no discomfort to the patient; it requires but a short stay in the hospital, and the results are often striking. The treatment of the inoperable case that has changed into the operable class by the use of radium is open to various opinions. Taylor would be willing to take a considerably increased primary risk if by doing so there is a correspondingly increased chance of a permanent cure; in fact, it is his custom, if the case is a good operable risk, to do either a simple or a modified radical hysterectomy.

Ectopic Adenomyomata of Uterine Type.—Of Clinical as well as pathological interest are the ten cases reported by MAHLE and MACCARTY (*Jour. Lab. and Clin. Med.*, 1920, v, 218), representing extra-uterine and extratubal tumors, which were diagnosed at the time of operation as adenomyomata. These growths contained glandular portions resembling typical uterine mucosa, surrounded by a fibrous connective tissue and smooth muscle stroma, the latter in varying amounts. The distribution of the tumors was as follows: Umbilicus, 1; abdominal wall, 2; sigmoid, 1; groin, 2 and rectovaginal septum, 4. They point out that, pathologically, extra-uterine adenomyomata are identical in appearance regardless of where they are found. They differ grossly from adenomyoma of the uterus, in that the cystic areas are larger and the contents darker brown. Grossly the tumors are solid, fibrous and of a light gray color. Here and there white bands extend into the tumor substance, while between these bands are areas, dark brown to almost black, varying in size from the head of a pin to cystic areas 1 cm. or more in diameter. On pressure a dark brown fluid exudes from the larger areas. Clinically, these tumors give no consistent group of symptoms on which an accurate diagnosis can be made. However, their location and their slow growth, extending over a period of years, suggests benign tumors. Further, the occasional relation to the time of menstruation, of pain or swelling of the tumor, or less frequently a bloody discharge, should be very suggestive of adenomyoma. Surgically, these tumors, regardless of their remarkable infiltrative characteristics, should be differentiated from malignancy. Especially is this true of tumors in the pelvis, adherent to the sigmoid or the abdominal wall or other structures. Adenomyomata may be recognized grossly in most cases by the fibrous

stroma, which contains cystic areas filled with a bloody, dark brown or serous fluid. The pathologist should distinguish adenomyoma from carcinoma by the regularity of gland structure with normal differentiated epithelial cells without mitoses, and, in most tumors, by the characteristic stroma surrounding the gland. He should also recognize that they are benign tumors, that they grow by invasion and do not metastasize. All of the cases here reported occurred in patients between the ages of twenty-nine and fifty years and pregnancy apparently had no influence, for 6 of the cases occurred in nulliparous women. Of the 10 patients 6 gave a history directly referable to the tumor; one stated that a tumor mass was found during operation elsewhere, for other symptoms of which the patient complained at that time. The remaining three patients had adenomyomata of the rectovaginal septum, which were so small that they were giving no trouble. In these cases the symptoms, when they were noted in the history, were enlargement, pain in the rectum or vagina at the time of menstruation, or a vaginal discharge.

Roentgenotherapy of Fibroids.—The results obtained in 400 cases of uterine fibroids that were personally observed while undergoing treatment by means of the roentgen ray is the basis of a communication from BECLERE (*Arch. Radiol. and Electrother.*, 1920, xxiv, 254). Of these patients approximately 25 per cent. were over fifty years old while about 11 per cent. were under forty years, so that the largest group (64 per cent.) were between forty and forty-nine years old. Concerning the size of the tumors subjected to treatment, he states that 85 per cent. of the tumors were palpable through the abdomen before treatment. His technic consists of weekly seances each of which consists of two successive radiations, the one to the right, the other to the left of the median line of the abdomen, immediately above the horizontal rami of the pubis. Occasionally, when the uterus is retroflexed, when the fibroid occupies the cavity of the sacrum or the neck of the uterus, a third radiation is directed on the sacral region. Finally, if the dimensions of the tumor demand it, the surface of the abdomen is divided not only into two, but into three, four and up to six circular areas, which in turn, serve as portals of entry for the rays. Each irradiation is localized to a circular surface of 10 cm. in diameter, by the aid of a cylinder of lead glass opaque to roentgen rays. A thin disk of wood is interposed between the localizing cylinder and the abdominal wall which depresses, levels the surface, and distributes over a considerable area the weight of the cylinder, and serves by a gentle compression, to reduce the distance between the ovaries and the skin. In 60 per cent. of the cases, the treatment has not required more than twelve to fourteen of these weekly seances, and has not lasted more than two and a half to three months. In only 4 cases has the treatment failed to avoid surgical treatment for the hemorrhage, while in the majority of cases the periods were suppressed without having appeared more than two or three times after the start of the treatment. This menopause, prematurely provoked, was usually definitely established, although in 12 per cent. of the cases, the suppression of the periods was only temporary and the periods returned after several months or years. In these cases further treat-

ment restored the menopause. In every case treated, not only was the growth of the tumor arrested but its size was diminished. Beclere firmly believes that the rays act directly on the fibroids, arresting their development and leading to a reduction in their size. He has found the treatment as efficacious before as after forty years of age and that it can be applied with equal success on either large or small tumors.

Relation of Pregnancy to Tumor Growth.—Having handled large numbers of mice with spontaneous tumors, SLYE (*Jour. Cancer Research*, 1920, v, 25) at once observed the great difference in the rate of tumor growth in the non-reproducing and in the reproducing females and she states that this same difference is noted in the rate of tumor growth in the non-reproductive and in the reproductive periods of the same female. In order to investigate this problem, thirty each of non-reproducing and of reproducing females with spontaneous tumors were selected. The tumors were all of the same type and of the same organ, viz., alveolar tubular carcinoma of the mammary gland, of which a daily observation is easily made. Without exception, the amount of tumor grown by a female while reproductive was strikingly less than during her non-reproductive period. Again, the amount of tumor grown by reproducing females was strikingly less than that grown by non-reproducing females. The normal course of these spontaneous tumors in mice that are not bred is very rapid, the mouse rarely living over six weeks and often less than a month after the appearance of her tumor. The tumors grow to a great size, frequently being as large as the body of the mouse. When, however, these tumorous mice are bred, the tumor scarcely grows at all during the reproductive period. The duration of the tumor is greatly prolonged, the mice frequently living nearly a year after the appearance of their tumors, during which time many bear from six to eight litters aggregating from twenty to thirty two young. When the mouse ceases reproducing, the tumors grow with tremendous rapidity and to great size, the female frequently surviving only six or eight days after the birth of the last litter. During this brief period the tumor grows to many times its size at the date of the last litter. In brief, during the six or eight days a mouse is non-reproductive, she grows enormously more tumor than during the eight months or a year while she is reproductive. From these observations, Slye concludes that cancer and reproduction, both being growth processes, draw upon the same energy residuum and are made possible by the same food, hence the food and energy used by one are withheld from the other. Therefore, if the female is constantly pregnant, energy and food are withheld from the tumor and it grows with extreme slowness. If there is a hiatus between pregnancies, or a termination of pregnancy, the energy which was running into reproduction is released and diverted into tumor which grows very rapidly. If tumor growth considerably antedates impregnation, the currents of energy are already being used for tumor growth and are with difficulty diverted for pregnancy, probably never wholly so. Hence when a female is well advanced in tumor growth before impregnation there are rarely any offspring brought to birth. When offspring are delivered, they are few, small, undernourished and rarely suckled.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Ultraspectroscopic Studies of Blood Serum.—In a physicochemical study of blood serum, TADOKORO (*Jour. Infect. Dis.*, 1920, xxvi, 1) shows that the antagonistic action of two salts, viz., $CaCl_2$ and NaCl, $ZnSO_4$ and $CaCl_2$ and $ZnSO_4$ and NaCl is due to the changes which they bring about in the colloidal state of the constituents of the serum. Examination of normal serum with the ultraspectroscope and the ultramicroscope showed that the presence of mikrons possessing Brownian movement was associated with a definite absorption band in the ultra-violet. When the serum was mixed with $ZnSO_4$ or CaCl its particles formed aggregates and became heterogeneous. Photographs of the spectra of these sera then showed that the absorption band tended to move away from the ultra-violet end of the spectrum. Addition of the second salt, *e. g.*, NaCl caused the aggregated particles to become free and homogeneous as in the normal serum. That is, the dispersion of the particles had been reversed and when this reversion occurred it was observed that the absorption band then moved toward the shorter wave length, or ultra-violet end of the spectrum. It is interesting to note that Tadokoro's conclusion that the antagonistic action of salts finds its explanation in changes in the degree of the dispersion of the colloidal particles confirms Clowes' interpretation of the same phenomenon, though the later investigator obtained his results mainly by means of surface tension measurements. In conjunction with NAKAYAMA, the author (*Ibid.*, p. 8) used the same method to investigate the changes produced in the colloidal state by immunization. Differences in the normal sera of the dog, guinea-pig, rabbit and horse were indicated by the fact that a similar absorption band, viz., between wave lengths 2950 and 2400 mikrons, could only be obtained by varying the dilution of each. When immunization was effected in these animals, comparison of the ultraspectrographs of the serum of each showed that the width and intensity of the absorption band in the immune serum were always greater than those found in the normal serum.

Dairy Infection with Streptococcus Epidemicus.—BROWN and ORCUTT (*Jour. Exper. Med.*, 1920, xxxi, 49) report a milk-borne streptococcus epidemic occurring during February, 1917, at Boston. The malady, which was most prevalent in children, began as a moderately severe sore-throat, attended by submaxillary and cervical lymphadenitis. A few cases experienced a peculiar nauseating nasopharyngitis, as well as otitis media. Recovery was sometimes quite slow and characterized by recurrent periods of high temperature. A very similar organism was isolated from the throats, tonsils and ears of the afflicted, from one cow in a herd of 112 and from eight of twenty-six employees of the dairy

These strains, isolated on 80 occasions, could not be distinguished morphologically nor biologically from one another. Cultures from adults in the families where the children were ill and from other cases of epidemic adenitis, not using the milk from this dairy, failed to reveal the presence of the Streptococcus epidemicus. The positive cultures from the cow were obtained from the udder. These appeared before the milk was grossly infected. The authors again emphasize the fact that infection of the cow's udder by Streptococcus epidemicus may persist for some time without gross evidence of mastitis and that the relative rarity of such milk-borne epidemics can be explained by the theory of Smith and Brown, in that streptococci of human, not bovine, origin are at fault. Streptococcus epidemicus in the blood agar plate, produces the beta type of hemolysis, similar to that of Streptococcus pyogenes, but usually slower in developing. The organism exhibits capsules in fresh surface colonies, where it resembles the growth of pneumococcus mucosus (type III), except that the latter produces the alpha appearance in blood agar. Although the organism was not particularly fatal to rabbits, an erysipelatous condition of the ears and an orchitis were the most conspicuous lesions. The epidemic ended immediately upon pasteurizing the milk and later, eliminating the affected cow from the herd. It is recommended as a minimum requirement for dairies producing raw milk that a regular examination of throat swabs from milkers and blood agar rather than plain agar for milk counts be employed.

A Method of Standardizing Bacterial Suspensions.—Many methods of determining the concentration of bacterial suspensions have been advocated. The more accurate methods involve much time and labor, while the simpler ones give only a rough approximation of the bacterial count. GATES (*Jour. Exp. Med.*, 1920, xxxi, 105) points out that if a wire loop is gradually introduced into a suspension of organisms in a test-tube and viewed by looking down into the tube through its mouth the depth at which the loop disappears will be determined by the opacity of the supervening column of the suspension. Experience has shown that, with a little practice, the depth of disappearance of the loop can be read within 1 mm., an error of less than 10 per cent.; nor, within certain limits, does the diameter of the test-tube nor the size of the wire loop affect the readings appreciably. The determination of the relation of the depth of disappearance to the concentration will give a quick and simple method of standardizing bacterial suspensions with a minimum of apparatus and manipulation. If a given suspension causes the loop to disappear at a given depth, in a dilution which is just half as heavy, the loop will not disappear at twice the distance, but at a point less than twice the distance. This discrepancy is due to the presence of a constant which is a function of the size and opacity of the individual bacteria in suspension. While the constant is the same for any series of readings on the same suspension, it varies with each suspension examined. The problem is to eliminate the constant, thereby bringing opacity and concentration into accord. Each of the observed readings on a single suspension is the sum of the corrected reading and the constant. The corrected reading for any suspension, by which its concentration may be compared with that of a standard suspension of the same organism, may be found by making a reading on the suspen-

sion, adding an equal amount of diluent, making a second reading and subtracting the first reading from the second. The higher the suspension is diluted, however, the less the error of observation. If a permanent standard is desirable which is then translated into terms of an accepted standard as the weight of dried bacterial substance on the number of organisms per c.c. the number of bacteria in any suspension can be found by inverse proportions. The apparatus can be very simple, consisting of a loop of nichrome wire thrust through a cork and measured with a centimeter scale laid against the test-tube. Another instrument is described by the author, who believes the method should be useful in the standardization of bacterial suspensions.

The Cultural Differentiation of Beta Hemolytic Streptococci of Human and Bovine Origin.—Although many good dairy products contain harmless hemolytic streptococci, it is of advantage to be able to identify those strains of hemolytic streptococci which are pathogenic for man. As no qualitative method for distinguishing hemolytic streptococci of human and bovine origin has been described, our ability to differentiate them has depended upon such quantitative reactions as agglutination and precipitation titer, the rapidity of hemolysis, the appearance of the colony in the blood agar plate, the rate of coagulability of milk and the action of a bouillon culture on blood corpuscles in suspension. BROWN (*Jour. Exp. Med.*, 1920, xxxi, 35) emphasizes the differential value of the action of streptococci of human and bovine origin on blood corpuscles in fluid media. Observations were made on twenty-eight carefully selected strains of bovine and human origin. The technic recommended by the Medical Department of the U. S. Army in 1918 for the identification of Streptococcus hemolyticus and a slightly different method of the author were employed with practically the same results. The latter consisted of diluting eighteen- to twenty-hour standard meal or beef infusion bouillon cultures to twenty times its volume with sterile 0.85 per cent. salt solution. One drop of sterile defibrinated horse, human, rabbit or beef blood is added to 1 c.c. of the diluted culture and incubated at 37° C. for two hours in the water-bath. As the test is purely quantitative, dilutions must be accurate. It was found that the strains of human origin hemolyzed the blood cells, while those of bovine origin did not and that the reaction depends upon the dilution of the medium rather than the dilution of the bacterial suspension. As a rule, in the blood agar plate, the bovine strains appeared as a small, clear, sharply defined central zone and a broad, outer, partly hemolyzed zone, some developing more slowly than the human strains which gave a clear, colorless, well-defined, completely hemolyzed wider zone of hemolysis. The pathogenic human strains of the beta type are of uniform size and character, whereas the bovine strains showed considerable variation. In some cases, however, it is very difficult to state positively the origin of the colony by its appearance in the blood agar plate. The titrable acidity after incubation for one week of the twenty-eight strains in bouillon plus 5 per cent. sterile horse serum and 1 per cent. saccharose, lactose, salicin, raffinose, inulin and mannite gave no characteristic reactions. The limiting hydrogen ion concentration of cultures in 1 per cent. dextrose bouillon after incubation of sixty-eight hours showed, as a rule, a higher reading with the human strains than the bovine. In milk, none of the human strains caused coagulation

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within twenty-four hours, while about 50 per cent. of the bovine strains did. The findings of Sherman and Albus, that cultures of Streptococcus lacticus reduce methylene blue in milk while those of Streptococcus pyogenes fail not only to do so but also to grow in this medium could not be confirmed in all instances and doubt as to the validity of selecting cultures by these workers is expressed. Of the twenty-eight strains, five were defined as irregular, the rest easily falling into the human or bovine groups. The author concludes that none of the procedures described serves by itself to differentiate streptococci of human or bovine origin with certainty, though each of them serves as a strong presumptive test.

Fungous Developmental Growth Forms of Bacillus Influenza.—The causative agent of epidemic influenza and the exact role of Pfeiffer's Bacillus influenzæ in this disease seems still far from solution. Recently, some investigators report success in their search for a filtrable virus. It would appear possible since familiar organisms, of supposedly fixed morphology, may assume a filtrable phase that this might be applicable to Bacillus influenzæ, and, for this reason, the morphologic stability of the organism is important. With these ends in view, WADE and MANALANG (*Jour. Exp. Med.*, 1920, xxxi, 95) attempted to determine the essential factors influencing the pathogenicity of certain strains of influenza bacilli obtained at autopsies and noted the familiar bacillus in but a simple form of an organism capable of complex development. Three strains were investigated, all of which failed to grow in the absence of hemoglobin. The optimum growth was on hot mixed (80°–90° C.) blood agar. One strain showed short, plump forms, while the other two tended to be longer. The pathogenicity to monkeys was lower than when first insolated. Toxin production was tested only for the first strain. The media consisted of beef infusion bouillon with Witte's peptone and sodium chloride to which was added laked or heated sheep or horse blood. Seeding was done by inoculating 0.1 to 0.2 c.c. of a saline suspension from a twelve- to twenty-four-hour agar growth into an ordinary tube culture. It was found that the bacilli abandoned their usual form and grew as a frank fungus of the Discomyces type. One strain yielded little of the filamentous growth in the cultures, but spore-like bodies which are structurally delicate were produced. These were, as a rule, greatly injured in ordinary preparations and were best demonstrated in Congo-red films. Conidial bodies, particularly when grown in symbiosis with streptococci, were abundant and apparently developed by direct transformation from short bacillary elements, as terminal knobs on simple rods or on short branches that might be likened to conidiophores, or as simple lateral buds. When grown with pneumococcus the bacilli disappeared in a few days. Though the original cultures were not dead, repeated subplants on blood agar from fluid cultures remained sterile, suggesting that the described forms are not due to involution but are the result of an adaptation to influences in the medium. Distinct stages in the depression of cultivability occur. A few attempts to perpetuate the fungous growth in the fluid media were made but subcultures have not developed to any great extent. The authors feel that they were working with pure strains of true influenza bacilli.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
MILTON J. ROSENAU, M.D.,
PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,
AND
GEORGE W. McCOY, M.D.,
DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

A Possible Mechanism for the Excitation of Infections of the Pharynx and Tonsils.—The vasomotor reactions of the buccal and pharyngeal mucous membranes to chilling of the body surface have been studied by MUDD and GRANT (*Jour. Med. Research*, 1919, xl, 53–101) in the hope of throwing light upon the mechanism by which chilling may excite infection of the mucous membranes by their indigenous bacteria. The authors devised simple wire "applicators" for holding in apposition with the skin or exposed mucous surfaces the terminals of thermopiles in circuit with a d'Arsonval galvanometer. From the thermometer and galvanometer readings the temperature of the surfaces beneath the thermopiles may be computed and temperature changes accurately followed. The cutaneous chilling of these experiments caused only inconsequential changes in blood temperature and pressure. Rate and depth of respiration were kept constant. Superficial temperature varied directly with rate of blood supply, and was an index of local vasomotor tone. This thermogalvanometric method, checked by observations of color change, showed that chilling of the body surface causes reflex vasoconstriction and ischemia—not, as hitherto assumed, congestion—in the mucous membranes of the palate, faucial tonsils, oropharynx and nasopharynx. With inhalation of amyl nitrite, skin temperature has always shown a sharp, transient rise. The mucous membranes, if relatively ischemic, show a rise parallel to the skin. If already hyperemic, local vasodilatation in the mucous membrane with amyl nitrite is more than counterbalanced by the lowering of general blood-pressure and the temperature falls. Scar tissue showed reflex vasoconstriction parallel to that of the neighboring skin. The earliest scar tested and proved to have vasomotor fibers was at the site of an operation performed a month before for removal of a keloid. In four instances exposure was followed by a "cold" or sore-throat. It does not seem improbable that the ischemia of the mucous membranes incident upon cutaneous chilling might so disturb the equilibrium between the host and the bacteria in the tonsillar crypts and folds of the pharyngeal mucosa as to excite infection.

Influenza at San Quentin Prison, California.—STANLEY (*Public Health Reports*, 1919, xxxiv, 996) reports three distinct epidemics of influenza in 1918, the first in April with 500 cases, the second in October with 69 cases, and the third in November with 59 cases. The mode of

conveyance was believed to be rather direct contact and it was thought that moving picture shows were responsible for considerable extension of the epidemic. Masking was tried, but appeared to have no influence on the spread of the infections. Tuberculosis developed in a number of cases. The following conclusions are drawn: (1) Each epidemic was apparently introduced by a recently infected entrant. (2) Close contact in crowded, poorly ventilated showrooms probably spread the infection. (3) The incubation period is from forty to sixty hours. (4) The second epidemic was less severe than the first, and the third less severe than the second, as shown by the number diseased, number of pneumonia cases, and number of deaths in each. (5) The infection spread in definite groups by close contact, as shown by its course in the rooms where night school was held. (6) The disease in the first and second epidemics attacked more prisoners between ages twenty to twenty-five, but in the third, more between the ages twenty-five and thirty as well as forty to forty-five became ill. (7) The most effective means available for combating the spread of the disease in this prison were hospitalization, quarantine, isolation, and closure of congregating places. (8) From the first epidemic it is seen that 5 per cent. developed tuberculosis. (9) It appears that those men who entered prison after the April epidemic were attached in greater numbers than those who had come before, although there were more of the latter than the former.

The Surgical Treatment of Typhoid Carriers.—NICHOLS, SIMMONS and STIMMEL (*Jour. Am. Med. Assn.*, 1919, lxxiii, 680–684) believe that the so-called urinary typhoid carriers are really kidney carriers, and can be cured by nephrectomy; that intestinal carriers are really bile passage carriers of two kinds, (*a*) cases in which the gall-bladder alone is infected and which can be cured by cholecystectomy, and (*b*) cases in which gall-bladder and bile passages are both infected, and which cannot be cured by surgical measures.

A Study of the Relation of Diet to Pellagra Incidence in Seven Textile-mill Communities of South Carolina in 1916.—GOLBERGER and WHEELER (*Public Health Reports*, March 19, 1920, pp. 648–708), to supplement their studies, chiefly experimental, of 1914 and 1915, began a study in the spring of 1916 in seven cotton-mill villages of South Carolina of the relation of factors of a dietary, economic and sanitary character to the incidence of pellagra. In this report they give the results of the first year's work with respect to the relation of household diet to pellagra incidence. They state that the selected communities were typical cotton-mill "villages," and were of about average size; none had over 800 or less than 500 inhabitants. Only the families of white mill operatives were included in the study. Pellagra incidence was determined by a systematic biweekly house-to-house search for cases carried on continuously from April 15, 1916, to the end of that year. Only patients with a clearly defined bilaterally symmetrical eruption were recorded as having pellagra. It is suggested that, clinically, pellagra includes at least two commonly associated but etiologically essentially distinct, though closely related, syndromes. The indications afforded by this study suggest that the pellagra preventive power of a milk or a meat supplement is due to the effect of a correction in the type of diet studied, of a deficiency supply either (1) of some

amino-acid or acids, (2) of the ash or of some of its constituents, (3) of some as yet unknown essential (vitamine?) or (4) of all or of a combination or combinations of some of these. Conversely, they suggest that the pellagra-producing dietary fault is the result of some one or of a combination or combinations of two or more of the following factors: (1) A physiologically defective protein (amino-acid) supply; (2) a defective or inadequate mineral supply; (3) a deficiency in an as yet unknown dietary essential (vitamine?). The somewhat lower plane of supply, both of potential energy and of protein, in the diets of the pellagrous households, though apparently not an essential factor, may, nevertheless, be contributory by favoring the occurrence of a deficiency in intake of some one or more of the essential dietary factors, particularly with diets having only a narrow margin of safety. The indications afforded by this study clearly point to an increase in the availability of milk, particularly by increasing cow ownership, and of fresh meat, by all-year-round meat markets as important practical measures of prevention and control in communities of the character studied. After the manuscript had gone to press, the authors received a copy of the "Report of a Committee on Enquiry Regarding the Prevalence of Pellagra among Turkish Prisoners of War" in Egypt (published February, 1919). Among the conclusions reached, the following are of most interest in the present connection: (*a*) "There is no evidence of the presence of any bacterial infection standing in etiological relation to pellagra; (*b*) there is no evidence of infection by any protozoal, spirochetal, or ultramicroscopic organism standing in etiological relation to pellagra; (*c*) pellagra is due to a deficiency in protein as gauged by its biological value."

Botulism: Protective Measures and Cautions from the U. S. Bureau of Chemistry, Department of Agriculture.—The Public Health Service (*Public Health Reports*, 1920, xxxv, 327) in an article based in part on the work of the Bureau of Chemistry, Department of Agriculture, presents the salient points in connection with the outbreaks of botulism that have been rather frequent in the United States in recent months. Ripe olives, commercially packed in glass, have been the cause of the majority of cases, though home-canned beans, asparagus and corn have accounted for some cases. Heating of food in the process of canning by immersion of the containers in hot water for a short time (one-half hour) does not suffice to kill the spores, but actual boiling of the material for such a period is sufficient. Food showing any evidence of spoilage should not be consumed.

Source and Significance of Streptococci in Market Milk.—JONES (*Jour. Exper. Med.*, 1920, xxxi, 347-361) states that the principal source of streptococci in milk is the cow's udder. The udder streptococci fall into two broad groups: those of the larger group agree in cultural characters and agglutination affinities with mastitis streptococci; the smaller group is composed of low acid-producing streptococci. The streptococci of the latter group produce clear zones of hemolysis about surface and deep colonies in horse blood agar plates. They attack dextrose, lactose, saccharose, and maltose, but do not ferment raffinose, inulin, mannite, or salicin. Acid production in dextrose by the members of this group is about the same as that produced

by human streptococci under the same conditions. The limiting hydrogen ion concentration for these pleomorphic udder streptococci in dextrose serum bouillon is within the limits of the limiting hydrogen ion concentration observed by Avery and Cullen for human streptococci. All the streptococci from the vagina, saliva, skin, and feces have been non-hemolytic. Those from the saliva form a heterogeneous aggregation in which individuals fermenting raffinose, inulin, and mannite predominate. From the skin a characteristic streptococcus has been found. It produces acid in dextrose, lactose, saccharose, maltose, raffinose, mannite, and salicin, but fails to acidulate media containing inulin. The fecal streptococci are characterized by the formation of large amounts of acid in dextrose, lactose, saccharose, maltose, raffinose, inulin, and salicin. Mannite is not fermented. Neither the fecal nor the skin streptococci have been isolated from bottled milk with any great frequency.

Filariasis in Southern United States.—Francis (*Hygienic Laboratory Bull.* 117, Washington, D. C., 1919) made a study of the prevalence of filariasis in the large southern cities, examining the blood of several hundred persons. Charleston, South Carolina, was the only city furnishing any considerable number of infestations, and in that city 77 persons among 400 examined harbored the parasites. The few infected persons found in other cities, Columbus, S. C., Beaufort, S. C., Jacksonville, Florida, and Tampa, Florida, probably were all contaminated in Charleston, S. C., or in Cuba where this infection is widespread. The lack of spread in communities other than Charleston, S. C., is attributed to failure of parasites to multiply in the mosquito, the small number of parasites imbibed, and the necessity for a male and female embryo to find lodgment in the same lymph gland, the limited number of homes where infection is likely, the chance that the larvæ may not have penetrated the skin, and finally the chance that in the mosquito the larvæ may not reach the proboscis. While these factors are operative in both the endemic foci and elsewhere, the occasional introduction of an infected person usually will fail to start the cycle which results in the perpetuation and spread of the disease. It is said that a shipload of slaves from an African filariasis focus was landed at Charleston many years ago and the present infestation is attributed to these. Work by Francis confirmed the previously demonstrated fact that Culex fatigans is the host of the Filariasis bancrofti. The writer recommends anticulex measures to abolish the mosquito pest and to do away with the risk of infections with filariæ. Very few of the cases showed chyluria or evidences of elephantiasis.

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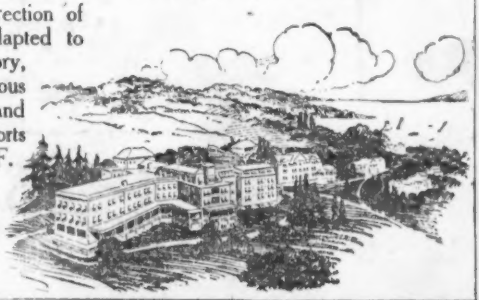
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